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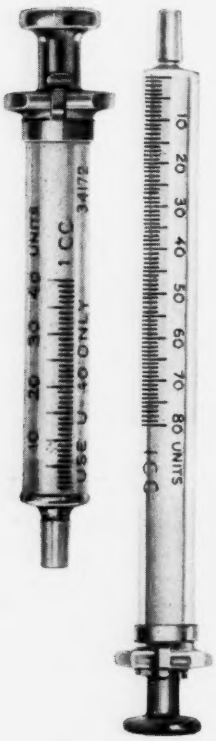

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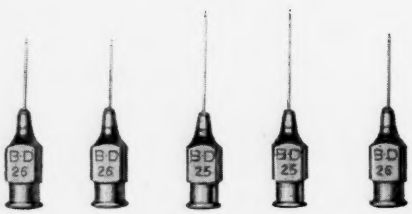

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Alpha Cell Cytotoxins

Their Influence on Carbohydrate Metabolism and the Effect of the Oral Blood Glucose Reducing Sulfonamides on the Islet Cells

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In recent years the literature on the function of the alpha cells of the Langerhans islands has repeatedly been reviewed.[32, 14, 111a, 37, 69] There is no doubt that they represent a system of cells *sui generis*. They probably are the site of production of glucagon[102, 44, 6, 6a] which has a hyperglycemic-glycogenolytic effect and like insulin enhances the peripheral glucose utilization.[28a] Alpha cell-like elements (the "X-cells") in the gastric mucosa differ from the pancreatic alpha cells by their staining and by their reaction to Synthalin A.[25, 69] The role of glucagon in the organism, under physiologic and pathologic conditions, is not yet clarified. The view that glucagon is a factor in the pathogenesis of diabetes mellitus is hypothetical. All studies reveal that glucagon like adrenalin, but unlike insulin, exerts only a transient effect. Thus far, experimental diabetes has neither been produced by partial pancreatectomy, nor by slow intravenous drip with glucagon.[96, 61, 45] Only recently evidence was obtained that glucagon may really be diabetogenic. In force-fed rats, a species notoriously resistant to diabetogenic effects, large doses of glucagon in oil have promptly produced average blood sugar levels from 350 to 450 mg. per cent, heavy glucosuria and a doubling of nitrogen excretion.[98a]

The fact that the alloxan diabetes in the dog improves after pancreatectomy, i.e., after removal of the alpha cells,[104] can easily be explained by a disturbance of food absorption. In the fasting state diabetes after pancreatectomy is definitely more severe than in alloxan diabetes.[85, 74] Blood sugar in alloxan diabetic rabbits is not reduced and insulin sensitivity remains unchanged after surgical removal of all alpha cells and alpha cell-like elements (resection of pancreas, stomach and intestine).[7] Alloxan diabetic dogs are even more sensitive to insulin than pancreatectomized dogs.[112]

Contradictory results were obtained by previous investigations of the islets in human diabetics. The view that diabetic hyperglycemia is due to an increase in alpha cells[30, 31] could not be supported.[54, 14, 5, 99, 80, 17] The glucagon content in pancreas of human diabetics is not different from that in nondiabetics.[67] Histologic findings as obtained with silver impregnations require further investigation since the methods for demonstration of the argyrophilic cells (Gros-Schultze, Bodian, Davenport) are not specific for staining of alpha cells in pancreas.[11, 12, 14, 17] In man markedly more silver cells are demonstrated than alpha cells[14, 26, 82, 17] and in rats, rabbits, and guinea pigs definitely fewer silver than alpha cells.[60, 110, 18] Only the various granular stains, as developed by Gomori, are adequate for demonstration of alpha cells in the pancreas.[51, 52, 53]

In the publications that have so far appeared referring to the quantitative changes of the alpha-beta-cell relation under the various experimental conditions (repeated insulin administration,[87] vagotomy and sympathetic block,[100] hypophysectomy[36, 110] and TSH administration,[103, 110]) determination of the size of the islets is lacking. It is therefore possible that the changes are only relative and due to a decrease of beta cells. Evidence of morphologic damage or destruction of the pancreatic alpha cells caused by a few chemical substances is therefore of special interest. In analogy to the experiment with alloxan, it appeared possible to study the reaction failures due to alpha cell damage and to correlate these with a lack of glucagon if no other metabolic and organic changes had occurred.

DIETHYLDITHIOCARBAMATE

Kadota and Midorikawa,[66] after administration of diethyldithiocarbamate (500-1,000 mg./kg. i.v.), observed initial hyperglycemia in rabbits in all cases with subsequent severe hypoglycemias in 4 of 17 cases. In these animals nuclear pyknoses, plasma degeneration and

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atrophy of alpha cells were found. This substance, however, is highly toxic and may interfere with various enzyme reactions, because of its reaction with many metals. Findings of the Japanese investigators could not yet be confirmed.[24, 56, 18] Davis[24] found inconstant beta cell changes in rabbits after administration of 600-1,000 mg./kg. diethyldithiocarbamate, but no specific necroses of the alpha cells.

COBALTOUS CHLORIDE

Van Campenhout and Cornelis[106, 107] observed that when guinea pigs were subjected to daily injections of 20 to 30 mg. $CoCl_2$ lasting several days, degranulation and vacuolization of alpha cells occurred, whereas the beta cells remained intact. The degree of alpha cell damage varies considerably from animal to animal, but in some cases almost all alpha cells are vacuolized (figure 1). Alpha cell death was observed only occasionally. There is considerable similarity of these alpha cell changes and their slow development with the hydropic degeneration of beta cells after abnormal stress. This allows the interpretation of a secondary degeneration probably due to some metabolic disturbance by this exceedingly toxic substance.[21] These changes are reversible.[21, 107] The hydropic alpha cells contain neither fat nor glycogen.[21, 69] The glucagon content of pancreas in the average is reduced by 60 per cent.[113, 29] Simultaneous histologic study of the extent of alpha cell damage, revealed that, in all cases with a marked degree of such damage, no glucagon could be extracted from pancreas.[6a] The blood sugar of guinea pigs, intoxicated with $CoCl_2$ however, does not decrease despite evidence of marked degree of alpha cell damage.[106, 21]

The investigations about the effect of $CoCl_2$ in rabbits are so far still contradictory. Goldner, Volk and Lazarus have described alpha cell damage after 25 to 40 mg. $CoCl_2$—which, in contrast to the findings in guinea pigs, becomes manifest within a few hours as nuclear pyknosis, plasma shrinking and cellular death.[49, 111, 65] Other authors were unable to demonstrate any degenerative alpha cell changes. These contradictions could perhaps be explained by the difference in crystal water present in $CoCl_2$ and thus represent a problem of dose. Fodden, who initially confirmed alpha cell damage in rabbits following $CoCl_2$,[38, 39] recently[40] found only inconstant alpha cell changes after $CoCl_2$. There was a more pronounced hyperglycemic and glycogenolytic effect from pancreatic extracts after administration of $CoCl_2$ in rabbits found normally.[41] Whether this striking result was due to the known high affinity of pancreas for $CoCl_2$ and thus represents a direct cobalt effect has not yet been investigated. Hypoglycemias, even after high $CoCl_2$ doses, have never been observed in rabbits, whereas initial hyperglycemia is constantly seen after intravenous[49] and/or subcutaneous[21] $CoCl_2$ administration, even with repeated administration. This hyperglycemia does not seem to be due to a release of glucagon from destroyed alpha cells since it is also demonstrable with definitely intact alpha cells after the administration of a low dose of 0.5 mg./kg. $CoCl_2$.[21] Initial hyperglycemia in rabbits is absent after preceding treatment with dihydroergotamine[28] or after adrenalectomy.[56] Chronic $CoCl_2$ administration for a period of two weeks with a dose of 12.5 mg./kg./day led to an increase of alpha cells in the rabbit.[56] Amelioration[2] of the alloxan diabetes in rabbits by $CoCl_2$—as assumed—could not be confirmed.[111, 39, 21]

In dogs, severe alpha cell damage and complete elimination of alpha cells after administration of 200 mg. $CoCl_2$, has been described.[72] The initial hyperglycemia corresponded to that found in rabbits and was demonstrable after pancreatectomy and partial evisceration. Hypoglycemias and improvement of the alloxan diabetes were not observed.[72] A normal hyperglycemic effect was obtained with pancreatic extracts from normal and alloxan diabetic dogs treated with $CoCl_2$[50] and from dogs after ligation of the pancreatic duct, after alloxanization and after administration with $CoCl_2$.[73] According to Fodden[40] the $CoCl_2$ damage in alpha cells of dogs, monkeys, cats, rabbits, rats and toadfish is inconstant and never complete. In teleosts (*Scorpaena scrofa L*) 100 to 150 mg./kg. $CoCl_2$ led to degranulation and vacuolization of alpha cells in the main islets and to a loss of the colloid globules as found in teleosts as well as to a loss of the hyperglycemic effect of tissue extracts.[90, 91]

The effect of $CoCl_2$ on alpha cells varies in the different animal species. Therefore the conclusion of Goldner, Volk and Lazarus based on the results of their careful experiments in rabbits and dogs, that the alpha cells do not produce glucagon and do not play an essential role in homeostasis of blood sugar, can only be accepted, if new experiments confirm the findings of these authors. At this time it has to be pointed out, that $CoCl_2$ causes generally accepted alpha cell damage only in guinea pigs. Complete vacuolization of almost all alpha cells in a few guinea pigs, (figure 1) with simultaneous complete loss of the glucagon in pancreas[6a] but without, however, occurrence of hypoglycemias remains a noteworthy fact, especially with reference to the Synthalin effect which will be discussed later.

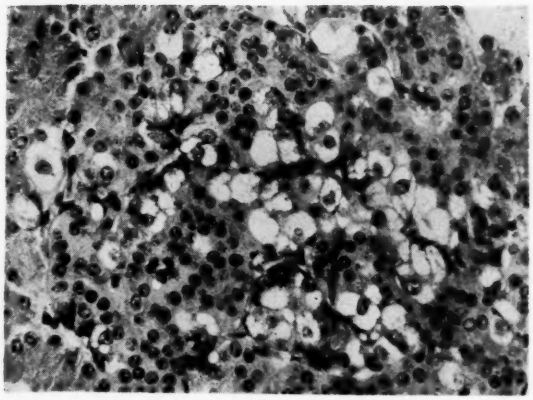


FIG. 1. Pancreatic islet of guinea pig after administration of 20 mg. $CoCl_2$ s.c. for 3 days. Blood glucose was 123 mg. per cent (when animal was killed) despite extreme vacuolization of most of the alpha cells and degranulation of the remaining alpha cells. (Staining with Azan after Gomori, Leica-photomicrograph, 300-fold enlargement.)

NICKELOUS CHLORIDE

$NiCl_2$ is more toxic than the chemically related $CoCl_2$. In the guinea pig degranulation and vacuolization even if not as marked as after $CoCl_2$ administration[89, 21] was reported after repeated daily S.C. injections of 20 to 30 mg. $NiCl_2$. Rats showed no alpha cell changes after $NiCl_2$ administration.[21] In the rabbit Kadota and Kurita[65] reported alpha cell destruction following administration of 15 to 20 mg./kg. intravenously similar to that seen after administration of $CoCl_2$. However, the beta cells were not fully intact either. $NiCl_2$ administration in rabbits results in an initial hyperglycemia, but never in hypoglycemias.[65] A dose of 4 to 6 mg./kg. i.v. has a definite hyperglycemic effect.[21]

DECAMETHYLENDIGUANIDIN (SYNTHALIN A)

The hypoglycemic effect of Synthalin A is well known through the investigations of Frank and collaborators.[42] This substance, therefore, was for some time employed as an oral antidiabetic drug. Because of its toxicity it is not used any more. Previous investigations pointed out an extrapancreatic mechanism of the Synthalin effect. Thus, in earlier studies severe liver cell damage, with glycogen depletion which followed Synthalin administration has been demonstrated.[101, 10] Synthalin, contrary to insulin, does not increase glycogen deposition in skeletal musculature. It also exerts a glycogenolytic effect on isolated liver of dog. Furthermore, it has a toxic effect on the metabolism of the cell and decreases oxygen consumption; hence lactic acid is formed from glucose by an anoxybiotic process.[110] It lowers the blood sugar level in the pancreatectomized dog[42, 95] and in the eviscerated animal and isolated muscle.[101, 10] Since under these conditions islet tissue is absent, the transmission of a blood sugar lowering effect via the Langerhans islets by stimulation of insulin production or loss of glucagon effect appears unlikely.

In 1952 Davis[24] reported that Synthalin A leads to hydropic degeneration of the alpha cells in rabbits. At the same time after an inconstant initial hyperglycemia,[10, 24, 39, 59] the known hypoglycemia with both hepatic and renal damage is seen. Alpha cell damage occurs only 15 hours after subcutaneous administration of 6 to 9 mg./kg. of Synthalin and its manifestations are degranulation and vacuolization of the cell without associating pyknosis of nuclei (figure 2) with the result that the number of alpha cells does not decrease.[24, 22, 23] On the other hand other authors reported a total loss of alpha cells in sporadic cases.[59, 55] The evaluation of larger experimental series reveals that the degree of the alpha cell damage in rabbits after Synthalin administration does neither parallel the moment of occurrence of hypoglycemia nor its degree, and only in sporadic cases are almost all alpha cells vacuolized.[24, 22, 23] The blood sugar increase and glycogenolytic effect of a pancreas extract of rabbits is lost after Synthalin intoxication.[41] Adrenalin[10] and glucagon[22, 23] have no blood sugar increasing effect in rabbits, intoxicated with Synthalin (figure 3). Hepatic glycogen depletion may be the cause for such.[22] The Synthalin effect is, however, not compensated with immediate and hourly injections

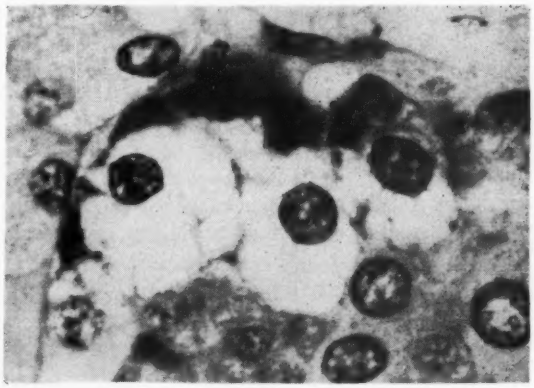


FIG. 2. Sector from pancreatic islet of rabbit which had received 6 mg./kg. Synthalin A s.c. No reduction of blood glucose was seen and animal was killed 36 hours later. A group of alpha cells with hydropic degeneration is seen (Azan staining after Gomori. Leica-photomicrograph, 1200-fold enlargement.)

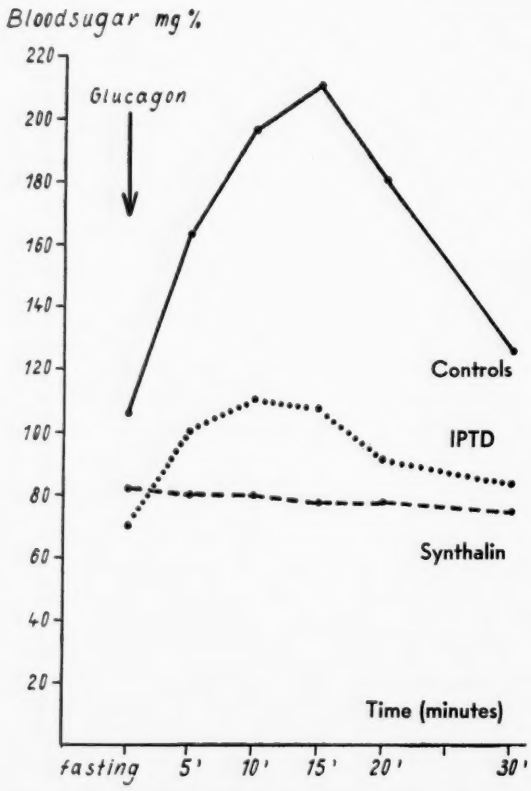


FIG. 3. Glucagon effect (Lilly) on blood glucose of normal rabbit (———) (15 μg./kg. glucagon, i.v.); of rabbit which had been intoxicated with Synthalin A (- - - - -) (30 μg./kg. glucagon i.v.) and of rabbits which had received 1 gm./kg. IPTD orally. (. . . . .) (15 μg./kg. glucagon, i.v.). Average curves from five respective experiments.

of 30 μg./kg. of glucagon (Lilly); on the contrary the manifestations of hypoglycemic shock are accelerated.[22, 23] Despite repeated injections of glucose, the animals die in hypoglycemic shock. Figure 4 demonstrates this fact and the simultaneously occurring only mild degree of alpha cell damage. The experiments clearly contradict the hypothesis that lack of glucagon causes synthalin induced hypoglycemia.

In alloxan diabetic rabbits after administration of Synthalin a decrease in blood sugar also occurs and a hydropic degeneration of the alpha cells of varying degree can be demonstrated.[39, 58, 59, 22, 23] Hypoglycemic shock can also be induced in alloxan diabetic rabbits.[59, 23] Synthalin leads to ketonemia and ketonuria in alloxan diabetic rabbits.[39] In the gastric mucosal x-cells which stain similarly to the alpha cells of the pancreatic islets without, however, being identical with them, no changes were seen in rabbits after Synthalin.[25]

Degranulation and vacuolization of alpha cells after Synthalin administration were reported, in addition to their occurrence in rabbits, in normal and also in diabetic rats[59, 23] and in guinea pigs.[97, 15, 23, 69] Rats are much less sensitive than rabbits and guinea pigs to blood sugar reaction and alpha cell changes.[69] Hamsters show no alpha cell changes at all, but severe renal damage.[69] Especially impressive is the hydropic degeneration of alpha cells after a three-day subcutaneous administration in guinea pigs (figure 5). The vacuolized alpha cells contain neither fat nor glycogen.[69, 18] There is no parallelism between the degree of alpha cell damage and decrease of blood sugar.[23] For evaluation of the hydropic degeneration of alpha cells induced by Synthalin it is of prime importance that in the guinea pig the damage is neither morphologically, nor in type or degree, distinguishable from the $CoCl_2$ effect (compare figures 1 and 5). The blood sugar level remains, however, normal in the animal poisoned with $CoCl_2$ whereas the Synthalin-treated animal dies in hypoglycemic shock.[15, 23] The hydropic degeneration of alpha cells therefore cannot be responsible for the drop in blood sugar following Synthalin administration. The morphologic picture and the slow development of the alpha cell changes following Synthalin make it much more likely that the vacuolization of the alpha cells represents a secondary degeneration similar to the one after administration of $CoCl_2$.[15, 23] No conclusion should be drawn that the Synthalin hypoglycemia and the alpha cell damage are related causally, since $CoCl_2$ does not cause a decrease in blood sugar but induces severe alpha cell damage in guinea pigs (see above), whereas hypoglycemia, due to insulin, is not accompanied by any alpha cell degeneration.[87, 15, 23] The vacuolization in adrenal marrow of rabbits and guinea pigs, following Synthalin administration,[22, 23] may be attributed to an abnormally increased adrenalin production due to prolonged hypoglycemias.

In view of the severe hepatic and renal damage,[24, 23, 69] Synthalin cannot be considered an elective mitotic alpha cell cytotoxin.[33, 98] This assumption is based on observations in newborn rats in whom Synthalin administration is supposed to result in a decrease of mitotic figures and mild disturbance of mitosis with absence of degranulation and vacuolization.[33, 98] Under the same experimental conditions, hepatic necroses following Synthalin have not yet been demonstrated in newborn rats; however, remarkable glycogen depletion as a sign of a direct effect of Synthalin on the liver has been found.[18]

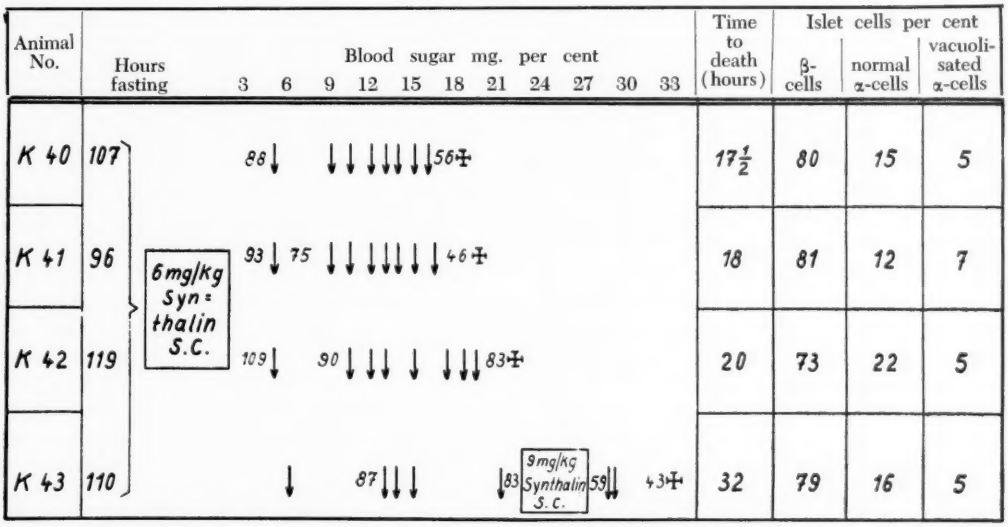


FIG. 4. Course of Synthalin poisoning in rabbits during intraperitoneal injections of 30 μg./kg. glucagon (Lilly) hourly.

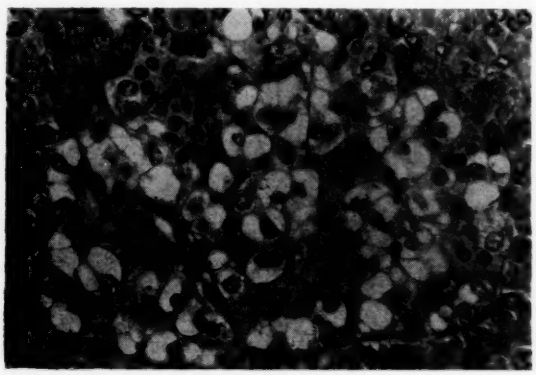


FIG. 5. Pancreatic islet of guinea pig, that received 3 mg./kg. of Synthalin A s.c. for 3 days and died in hypoglycemic shock (blood glucose 26 mg. per cent) on the third day. Vacuolization of alpha cells to a high degree, morphologically no difference to figure 1, same technic.

SECONDARY ALPHA CELL CHANGES IN LIVER DAMAGE

Degranulation and vacuolization of alpha cells in the course of fatty degeneration has been repeatedly described.[48, 108, 109] These alpha cell changes can be demonstrated in rats after fattening with oil, and after *Amanita phalloides* and $CHCl_3$ intoxication with a concomitant activation of the adrenal cortex.[108, 109] A mere activation of the cortex alone by unspecific stress has no influence on the alpha cells.[15, 23] Starting from the marked toxic effect of Synthalin on the liver in guinea pigs, (diffuse fatty degeneration, glycogen depletion, and peripheral lobular necrosis with relatively constant alpha cell damage) the effect of various hepatic toxins on alpha cells of the guinea pig was studied systematically.[15, 23] Consequently, after administration of phosphorus, carbon tetrachloride, chloroform and ethionin, degranulation and frequently vacuolization and a marked mitotic activity of alpha cells were seen almost always in addition to the known hepatic changes. The alpha cell changes can be interpreted as a sign of stimulation (secondary degeneration) caused by disturbance of liver function. Alpha cell stimulation is not induced by every liver damage. Stimulation, for instance, is absent in allyl formate intoxication and in the fatty liver of scurvy.[23] Only in the terminal stage of phosphorus intoxication in guinea pigs may a drop in blood sugar or hypoglycemic shock be seen. This, however, is not always apparent.[15, 23] The alpha cell stimulation in certain disturbances of hepatic function is suggestive of the essential role that glucagon plays in hepatic metabolism. Glucagon (Lilly) has no protective function for the liver of guinea pigs against hepatic poisons.[23] A lipotropic effect of glucagon in rats intoxicated with CCl_4 was not demonstrable.[23]

BLOOD GLUCOSE REDUCING SULFONAMIDES

The substances that will be discussed below have recently aroused wide interest because, due to their

blood sugar reducing properties, even in minimal, i.e., apparently nontoxic doses, they are suitable as oral antidiabetic drugs. According to the present investigations, the blood sugar reducing effect of various sulfonamide derivatives is probably based on the same principle. They have proved effective in certain human diabetics when given in the same dose. Since the common mode of action has so far not been clarified, the experimental results about the individual substances will be discussed separately.

P-aminobenzolsulfonamidisopropylthiodiazol (*IPTD*)

In 1942 Janbon and co-workers[62] made the interesting observation that IPTD, a bacteriostatic sulfonamide, initiates severe hypoglycemic reactions in patients in a reduced nutritional state. Further experiments in healthy persons revealed that a blood sugar reducing effect of this substance is proportional to the sulfonamide level.[63, 64] Loubatières did extensive experimental work in dogs and rabbits on the mode of action of the reduction of blood sugar by IPTD.[75, 76, 77, 78] IPTD (0.4 gm./kg. given orally or subcutaneously as sodium salt) leads to regular and reversible reduction in blood sugar which paralleled the sulfonamide level in the blood. Repeated, larger doses resulted in a severe glycopenic condition in dogs. IPTD administration over several days markedly increased hepatic glycogen content. In the pancreatectomized dog and in the idiohypophyseal diabetes in dog, IPTD was ineffective, whereas in the partially pancreatectomized animal with 5/6 to 9/10 resection a definite effect on blood sugar was proved. In moderately severe alloxan diabetes of the rabbit glycosuria could be suppressed throughout the period of administration of IPTD. After the drug was discontinued glycosuria recurred to the same degree. Loubatières concluded from his experiments that IPTD stimulates insulin production of the beta cells.

The observation that IPTD (intravenously) reduces blood sugar in mild alloxan diabetes of the dog but is ineffective in severe alloxan diabetes points into the same direction.[4] Von Holt et al.[58, 59, 55] later described alpha cell damage and total cell destruction following IPTD (1 gm./kg.) orally and intraperitoneally in rabbits and rats. These authors explained the blood sugar reducing effect of the sulfonamide in normal and alloxan diabetic animals by an uncompensated insulin effect following failure of alpha cells. After treatment with IPTD, alloxan produced diabetes in 50 per cent of the cases; 25 per cent died during the initial hypoglycemia and 25 per cent never became diabetic.[59] The conclusion drawn from this observation was that absence of a terminal diabetic hyperglycemia was due to antecedent destruction of the alpha cells by IPTD.[59] This, however, is not correct. The success quotient of diabetic animals corresponds much more with that which one can expect in alloxanization of a large number of rabbits.[94]

The initial hyperglycemia following IPTD administration in rats could not be correlated with release of glucagon from the destroyed alpha cells since it did not occur after adrenalectomy.[57] There are contradictory reports as to the fate of liver glycogen after IPTD. Whilst deposition of glycogen was described in dogs[75, 76] and in rabbits the glycogen content remained normal or was even elevated,[22,23, 83] in rats a decrease of glycogen was seen.[57] In rabbits liver glycogen can be mobilized by glucagon under IPTD but the increase in blood sugar is definitely less than in the normal animal (figure 3).[22] Alpha cell damage as plasma clumping and cell shrinkage was partially confirmed[23, 48] but there was no hydropic degeneration as is typical for $CoCl_2$ and Synthalin intoxication.[23] A reduction of the number of alpha cells was found in only 5 of 14 rabbits after 1 to 2 gm./kg. IPTD orally. Correlation between extent of alpha cell damage and reduction of blood sugar was not demonstrable. Preceding liver damage by CCl_4 increased the blood sugar reducing effect of the IPTD.[23] In normal and alloxan diabetic rats 0.75 to 1.0 gm./kg. IPTD given intraperitonally resulted merely in degranulation of alpha cells; however, no degenerative changes and no reduction of their number was noted.[46] A definite blood sugar reducing effect of IPTD in alloxan diabetic rats could not be proved.[13] Activity of alkaline phosphatase in the alpha cells of rats was not altered after IPTD.[20]

Therefore, the regular reduction of blood sugar after administration of IPTD can hardly be explained by its alpha cell damage, for the damage is inconstant and demonstrable only with high doses of the drug. This probably is a side effect and this is supported by the observation that IPTD in certain diabetics in man already exerts a favorable effect on hyperglycemia and glycosuria in the low dosage of 25 to 50 mg./kg.[78, 79, 71, 18]

N-sulfanilyl-N_2-N-butylcarbamide (BZ-55) *

Clinical trial of the sulfonamide BZ-55 revealed a noteworthy blood sugar reducing effect which initiated testing of this drug as an oral hypoglycemic agent. In certain diabetics a very satisfactory effect on hyperglycemia and glycosuria was found with dosages of 20 to 40 mg./kg.[43, 9, et al.] The blood sugar reducing effect

* Nadisan(R) (C. F. Boehringer, Mannheim, Germany). Invenol(R) (Farbwerke Hoechst, Frankfurt/M., Germany). Carbutamide (Eli Lilly and Company, Indianapolis, Indiana).

paralleled the sulfonamide level in the blood as found by clinical investigation[43] and experimental study.[1] In rabbits the glucose tolerance test under BZ-55 shows the same results as in normal animals.[1] In the starving rabbit hepatic glycogen content under BZ-55 increases in spite of reduction of blood sugar whereas glycogen content in muscles remains unchanged in contrast to the effect of insulin.[8, 8a] BZ-55 in the moderately severe alloxan diabetes decreases the blood sugar in rabbits[1] whereas it is ineffective in severe alloxan diabetes.[1, 8, 8a] Mirsky[86] in addition reported about inhibition of insulinase in vivo and in vitro. In rabbits and rats after extremely high doses of BZ-55 (1.5 to 3.5 gm./kg.) in 50 per cent of cases degenerative changes were reported in a few alpha cells.[35] This observation, however, does not suffice to explain the reduction of blood sugar which regularly can be produced with even markedly smaller doses. In three human diabetics treated with BZ-55 no alpha cell changes were found.[34]

The oral, intraperitoneal or intravenous administration of BZ-55 1 gm./kg. when given for a short period or for several weeks resulted in no degenerative changes of the alpha cells in rats. The beta cells were markedly degranulated and after several weeks hypertrophy of the islets was seen. It is concluded from these morphologic findings in rats and from the absence of a reduction of blood sugar in steroid or in alloxan diabetes in rabbits that BZ-55 stimulates beta cells, i.e., increases insulin production.

The reduction of blood sugar by BZ-55 was also demonstrable in the adrenalectomized and hypophysectomized rat.[69]

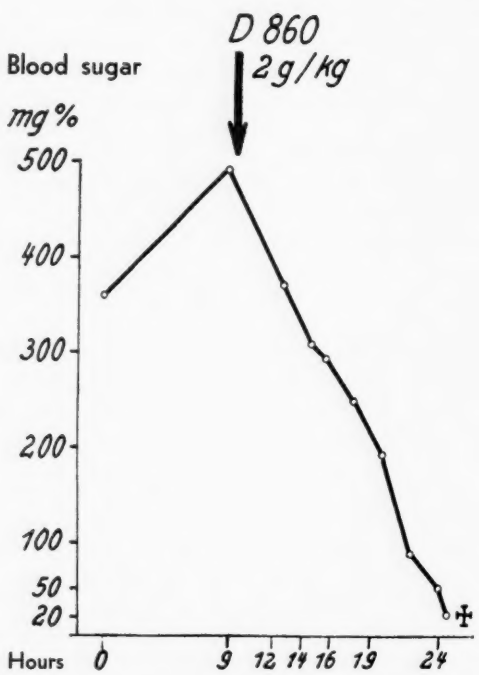
New results of the Toronto group indicate the possibility that BZ-55 acts in more than one way in reducing the blood sugar level. It was shown that BZ-55 inhibits some metabolic processes in certain liver preparations in vitro.[13a] The administration of BZ-55 orally to normal rats for periods of three weeks led to a significant depression in the glucose-6-phosphatase activity of the liver.[54a] Intravenous injection of BZ-55 in rats caused a reduction in the rate of absorption of glucose from the gut.[43a] The administration of BZ-55 in rats by mouth for three to four weeks induced a significant increase in islet tissue. This would suggest that the islets of Langerhans have been stimulated by BZ-55.[1a] In three pancreatectomized dogs and in one dog with metahypophyseal diabetes given insulin the administration of BZ-55 reduced the sugar excretion, the blood sugar and the insulin requirements.[100a, 10a] A blood sugar lowering effect of BZ-55 alone (0.8 to 1.5 gm./kg. intravenously) in totally pancreatectomized dogs was recently reported.[14a]

N-[4-methyl-benzolsulfonyl]-N¹ butylcarbamide (D 860*)

D 860 differs from BZ-55 merely by substituting the amino-group in the benzol ring for a methyl group.[27] The consequence of this substitution is an almost complete loss of the bacteriostatic effect of D 860 towards gram positive organism and *Bacterium coli*.[93] D 860 in treatment of diabetes with sufficient endogenous insulin has proved to be of very great value when given in the same doses (20 to 40 mg./kg.) as IPTD and BZ-55.[103, 83, 68]

In animal experiments the blood sugar reducing effect of D 860 parallels its blood level.[84] The substance does lead to glycogen deposition in the liver when given in nontoxic doses[3, 84, 8a, 18] and in higher doses it does not result in excessive glycogen depletion.[3, 19] The muscle glycogen, however, does not increase so that there is no similarity with the insulin effect.[84, 8a, 18] After D 860 the glucose tolerance test in rabbits has the same results as in the normal animal.[19] Glucagon hyperglycemia in rabbits treated with D 860 is significantly diminished compared to control groups.[19] Hypoglycemic shock as frequently seen in fasting rabbits after administration of 0.5 to 1 gm./kg. of D 860 could always be eliminated by intravenous administration of glucose, but not regularly by intravenous glucagon (Lilly).[19] D 860 was ineffective in pancreatectomized dogs[70] and in severe alloxan diabetic (acidotic) rabbits.[18a] In the latter instance frequent alpha cells could still be demonstrated in rests of islets. In contrast, 1 gm./kg. of D 860 given orally to moderately severe alloxan diabetes of rabbits without acetonuria led to definite though transient reduction of blood sugar and to a decrease of glycosuria. This, however, recurred after the drug was discontinued. In mild alloxan diabetes with a tendency to spontaneous remissions, diabetic symptoms will finally subside after D 860 administration.[18a] It is interesting that with high doses of D 860 (2 to 3 gm./kg.) in moderately severe but constant alloxan diabetes in rabbits fatal hypoglycemic shock which is similar to that produced by administration of Synthalin can be induced (figure 6). Since in the alloxan diabetic animal endogenous insulin is markedly diminished and beta cells are already maximally stimulated, the findings seem to argue against stimulation of insulin production by D 860 and favor a direct action on the carbohydrate metabolism.[18a] Re-

* Rastinon(R) (Farbwerke Hoechst, Frankfurt/M., Germany). Artosin(R) (C. F. Boehringer, Mannheim, Germany). Orinase(R) (Upjohn Company, Kalamazoo, Michigan).



Rabbit (KA9) constant alloxan diabetes without acidosis since 61 days.

FIG. 6. Reduction of blood glucose in a rabbit with constant alloxan diabetes on 62nd day after oral administration of 2 gm./kg. D 860. Death in hypoglycemic shock.

duction in blood sugar by D 860 occurs independently from the hypophyseal and adrenocortical system since it remains intact in hypophysectomized and adrenalectomized rats.[3]

In vitro experiments have shown that D 860 in small concentration does not influence O_2 consumption of liver homogenate and that activity of the succinodehydrogenase is not influenced.[3] With higher concentrations an inhibitory effect on catabolism of glycogen to free glucose and inhibition of the aerobic phase of the glycolysis was found in hepatic slides.[88] Insulinase was reported to be inhibited by D 860 in in vitro and in vivo experiments.[86] However, therapeutic concentrations of sulfonylureas do not inhibit the activity of the insulinase and glucose-6-phosphatase and have no effect on the glucose output of liver slices in vitro.[107a] On the other hand, the glucose output by adrenalin from liver slices was markedly reduced in the presence of sulfonylureas, which points to blocking of the liver phosphorylase-system.[107a]

Histologic examination of pancreatic islets revealed no changes of the alpha cell in rabbits after oral administration of 1 to 2 gm./kg. D 860 even following severe hypoglycemic shock.[19] The reaction to alkaline phosphatase in the alpha cells of rats was not changed by D 860.[20] In long-time experiments with rabbits after administration of a daily dose of 1 gm./kg. D 860 over a period of sixty-eight days, the alpha cells were occasionally diminished somewhat in size and number. The beta granules in aldehydefuchsin-preparation decreased and frequently the beta cells showed complete degranulation. This degranulation of beta cells may be considered as functional rest in analogy to the known repeated insulinization experiments.[5, 92, 47] Interpretation of beta cell degranulation as a sign of stimulation is contradicted by the slow development and the response of the beta cell zinc under D 860. A few hours after administration of D 860 the zinc in the beta cells can be demonstrated histochemically to an increased extent. In "subacute" experiments (five to eight days) it is present in normal amount.[81] Functional rest of the beta cells can only be understood if a primary blood sugar reducing or an insulin potentiating effect is attributed to D 860. For full development of this effect a certain amount of endogenous insulin is required as shown by the aforementioned experiments in alloxan diabetes of various degrees in rabbits.[18a]

No morphologic changes of alpha cells were seen in alloxan diabetic rabbits after administration of D 860. Even in cases of hypoglycemic shock following administration of D 860 in a previously constant alloxan diabetes the alpha cells were intact.[18a]

In six human diabetics who had been treated with D 860 over a period of six months and who died from other causes, no alpha cell changes were found. The beta cells showed a degree of granulation which was not different from that found in untreated diabetics, thus demonstrating that they were not specifically stimulated. Diabetics who did not respond to D 860 therapy had only a few beta cells and thus suffered from a remarkable lack of insulin.[16]

SUMMARY

1. In a critical review of the literature it is shown that thus far there is no definite evidence for the assumption that the alpha cells of the Langerhans islets, which probably produce glucagon, play an essential role in the blood sugar homeostasis and in the pathogenesis of diabetes mellitus or in the etiology of diabetic hyperglycemia. The investigations with the hitherto known alpha cell cytotoxins cannot lend support to such hypotheses since their effect on blood sugar can be explained by extrapancreatic mechanisms.

2. The reports as to the extent of alpha cell damage following diethyldithiocarbamate and cobalt chloride in rabbits are still contradictory. However, clearcut and reproducible alpha cell damage is described by many authors following administration of $CoCl_2$ in guinea pigs and after Synthalin A administration in rabbits and guinea pigs. In these animals both substances result in a morphologically identical vacuolization of alpha cells (secondary degeneration?) and a decrease of content of glucagon in pancreatic extract. Blood sugar reductions, however, only occur after Synthalin. A parallelism between the very varying degree of alpha cell damage and blood sugar reduction after Synthalin does not exist. The previously known experimental results are suggestive of an extrapancreatic site of action of the Synthalin in the carbohydrate metabolism.

3. Experiments producing various types of liver damage led to secondary alpha cell changes similar to those caused by the likewise strongly hepatotoxic Synthalin which points to a close correlation of alpha cells and hepatic metabolism.

4. The recently introduced antidiabetic sulfonamide derivatives with their blood sugar reducing properties do not exert their effects through alpha cell damage. The alpha cell changes as seen occasionally when these are given in high doses in the animal experiments probably are a side effect. In human diabetics following sulfonamide treatment no alpha cell changes were observed. Stimulation of insulin secretion by the sulfonamides is not settled. A series of findings rather points to a direct interference of these substances with the carbohydrate metabolism which is not identical with the insulin effect.

SUMMARIO IN INTERLINGUA

Cytotoxinas Afficente le Cellulas Alpha del Insulas de Langerhans: Lor Influentia Super le Metabolismo del Hydratos de Carbon e le Influentia Exercite Super Illos per le Sulfonamidos Oral que Reduce le Glucosa del Sanguine

1. Es demonstrate per un revista critic del litteratura que usque nunc il existe nulle supporto conclusive pro le supposition que le cellulas alpha del insulas de Langerhans, que probabilemente produce glucagon, ha un function essential in le homeostase del sucro sanguinee e in le pathogenese de diabete mellite o in le etiologia de hyperglycemia diabetic. Le investigationes executate con le usque nunc cognoscite cytotoxinas afficente le cellulas alpha non supporta ille hypothese, proque lor effecto super le sucro del sanguine es explicabile per mechanismos extrapancreatic.

2. Le reportos relative al grado del lesion del cellulas alpha post le administration de diethyldithiocarbamato e de chlorido de cobalt in conilios es ancora contradictori. Tamen, clar e reproducibile lesiones del cellulas alpha es describite per multe autores como resultato del administration de $CoCl_2$ in porcos de India e de Synthalina A in conilios e porcos de India. In iste animales, le duo mentionate substantias resulta in un morphologicamente identic vacuolisation del cellulas alpha (degeneration secundari?) e in un reduction del concentration de glucagon in extractos pancreatic. Sed reductiones del sucro sanguinee occurre solmente post administrationes de Synthalina A. Nulle parallela existe inter le variabilissime grado del lesion del cellulas alpha e le reduction del sucro sanguinee post le administration de Synthalina. Le previemente publicate resultatos experimental suggere un sito extrapancreatic pro le action de Synthalina in le metabolismo de hydrato de carbon.

3. Le production experimental de varie typos de lesion hepatic resultava in lesiones secundari del cellulas alpha, simile al lesiones causate per Synthalina (que es equalmente multo hepatotoxic). Isto pare signalar un stricte correlation del cellulas alpha e del metabolismo hepatic.

4. Le recentemente introducite sulfonamidos antidiabetic (con lor influentia reductori super le sucro de sanguine) non exerce lor effectos via le lesion del cellulas alpha. Le alterationes del cellulas alpha que es a notar a vices quando ille sulfonamidos es administrate in experimentos animal in sufficientemente alte doses es probabilemente effectos lateral. In diabeticos human, nulle alterationes del cellulas alpha ha essite observate post le administration de sulfonamidos. Il non es probabile que le sulfonamidos effectua un stimulation del secretion de insulina. Varie datos indica plus tosto que iste substantias affice directemente le metabolismo del hydratos de carbon, lo que non es identic con le effecto de insulina.

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Activators and Inhibitors

Specific activators and inhibitors of enzyme reactions remain as the major agents suggested to be responsible for the alteration of metabolic reaction rates in vivo. A number of drugs are believed to inhibit enzymes by competition with their normal substrates, but the hormones are the most important of the physiologically occurring regulators to be considered in this connection. Barron believed that enzymes were generally present in tissues in tremendous excess over the functional requirements, but that their reactions were inhibited to an extreme degree by hormones and other regulators. Modulations of the degrees of inhibition were believed to accomplish metabolic regulation. An erroneous comparison between the rate of the reaction catalyzed by a *mole* of pure enzyme and by a *gram* of tissue gave rise to this belief in a million-fold excess of enzymes in tissues. The general experience has been that the rates of reactions in vivo and in vitro are more nearly of the same order of magnitude, whenever these rates can be compared. The possibility remains that regulation could be accomplished by modulated inhibitions, of a less extreme degree, if specific inhibitors could be demonstrated.

From "Enzymatic and Metabolic Adaptations in Animals" by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* *36*:164-254, 1956.

On the Action of BZ-55 and D-860 in Pancreatectomized Dogs

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In the studies of Loubatières[1] (1955) on the effects of IPTD or 2254 RP and in the subsequent work on the possible mechanism of action of BZ-55 it was generally agreed that these compounds did not decrease the blood sugar concentration in completely pancreatectomized dogs. This question was re-examined and it was observed that a dose of 0.1 gm. BZ-55 or D-860 per kg. bodyweight did potentiate the effect of an insulin dose injected within the last twenty-four hours. Although others have very recently reported similar findings (Sirek et al.[2] 1956; Kirtley et al.[3] 1956), the treatment brought about symptoms which indicated a toxic effect of the compound upon the liver, a fact which may warrant a publication of our independent studies.

EXPERIMENTS WITH BZ-55

The effect of BZ-55 was studied in four pancreatectomized dogs. Dog no. 20 was given 44 i.u. Iso-Insulin Novo daily with the effect upon the blood sugar seen in figure 1 (curve A). After an eight-day control period, 2.0 gm. BZ-55 were administered orally at 4 p.m. every day in addition to the insulin. The fasting blood sugar decreased in the subsequent days (cf., 1x, 2x, 3x, 4x and 5x, figure 1) and finally, on the fifth day, the blood sugar remained around 100 mg. per cent without any insulin injected on that day (curve B, figure 1). It was not until forty-eight hours after the last dose of insulin that hyperglycemia occurred (curve C, figure 1). On continuation of the combined BZ-55 and insulin treatment, the dog lost its appetite completely and was almost lethargic at the time it died, after a total of fourteen days of treatment. A post-mortem examination revealed a high degree of fatty degeneration of the liver and extensive hemorrhages in the small and large intestines. Bacteriological tests did not indicate that these changes were caused by an infection resistant to BZ-55 but rather by the pronounced fall in the clotting time of the blood indicated by extremely low prothrombin values. In dog no. 26 which had 2.0 gm. BZ-55 for five days and 1.0 gm. for eight days, the initial symptoms were the same. The prothrombin value fell from the normal range of from 140 to 160 per cent to between 15 and 20 per cent (compared to human blood) in the course of thirteen days of treatment, and the serum total protein was 4.0 per cent and albumin 1.0 per cent. As the dog refused food altogether and developed an icterus with 5.8 mg. per cent bilirubin in plasma, the BZ-55 was omitted and intravenous injections with glucose solutions and protein hydrolysates were given daily for eleven days. Two months later the dog appeared healthy, with a serum protein of 5.3 per cent and 3.6 per cent albumin and a normal prothrombin value.

Dog no. 27 was only given two intravenous injections of 2.0 gm. BZ-55 with a five-day interval. Figure 2 demonstrates their effect upon the blood sugar concentrations with and without a previous injection of insulin. In this case exactly the same toxicological effects were observed as in no. 26, but recovery was more rapid. Approximately two months after recovery, this dog was again given 1.5 gm. BZ-55, this time orally once a day. In the course of three days the prothrombin value fell to 6 per cent and remained low until the dog died after ten days of BZ-55 treatment. The blood showed an increased destruction of erythrocytes (2.4 mill. per cmm.; hematocrit 19.7) and there was 1.1 mg. per cent bilirubin in the plasma. In addition a slight degree of leucopenia (7,700 per cmm.) and granulocytopenia (49 per cent) was observed. Autopsy revealed large subperitoneal and submucosal hemorrhages in the intestinal tract and degeneration of the liver.

Another dog, no. 28, was given 1.0 gm. BZ-55 daily six days before and thirteen days after pancreatectomy together with 15 i.u. Insulin Novo Lente. Icterus appeared also, and the prothrombin value decreased to 12 per cent. On the thirteenth day the dog was killed and at that time the total serum protein was 4.0 per cent, albumin 0.73 per cent, prothrombin 5 per cent, and there was 3.9 mg. per cent bilirubin in plasma. Hematological examinations demonstrated also in this dog a leucopenia (4,500 per cmm.) and a slight granulocytopenia (51 per cent). Autopsy showed a slight degeneration of the liver, heavy icteric pigmentation of all tissues, large

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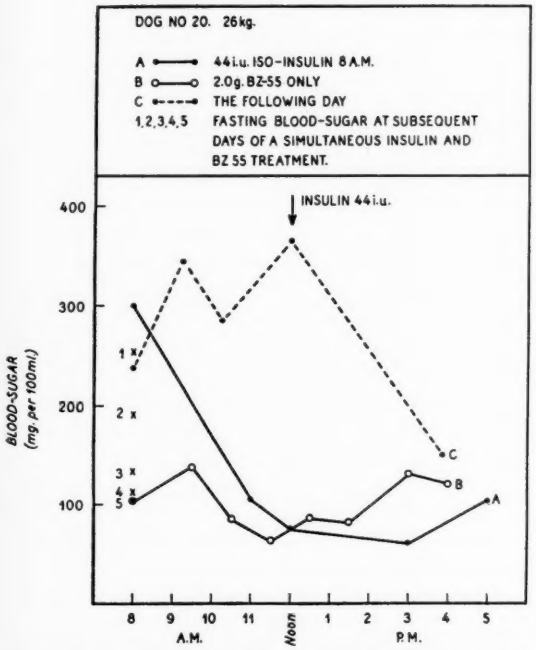

FIG. 1. Curves showing daily blood sugar concentrations in a pancreatectomized dog treated on five consecutive days as indicated: Curve A: 44 i.u. Iso-Insulin NOVO 8 a.m. 1x, 2x, 3x, 4x: fasting blood sugar at subsequent days on insulin and 2.0 gm. of BZ-55.

Curve B: 5x, only 2.0 gm. of BZ-55. Curve C: 2.0 gm. BZ-55 and forty-eight hours after the last dose of insulin, but where insulin was again given at noon.

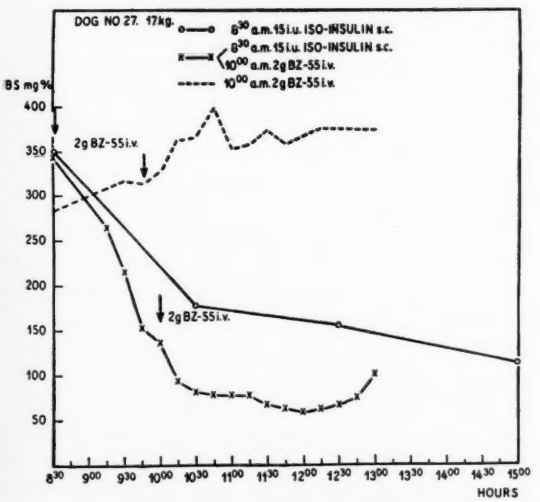

FIG. 2. Blood sugar curves demonstrating the effect on a pancreatectomized dog of an intravenous injection of 2.0 gm. BZ-55 with and without a previous injection of 15 i.u. Iso-Insulin NOVO.

ecchymoses in the small intestines and a pronounced submucosal edema.

Histological examinations revealed a varying degree of fatty infiltrations in the liver of all these dogs, especially in the periphery of the lobuli. Degeneration of the nuclei and cellular infiltration were not observed. The general structure of the kidneys appeared to be normal, but in all of the dogs fed BZ-55, a fine, granular, neutrophilic mass was observed in several of the renal corpuscles. It seemed to be the "parietal" part of the capsular epithelium which had proliferated and was partly exfoliated into the capsular space. Mallory's stain clearly demonstrated the proliferation of both this epithelium and the glomerular basement membrane. The cells of the proximal convolutions had lost their brush border and the cytoplasm was finely vacuolated. An amorphous, vacuolated mass was seen in the lumen of this section of the tubules. While the descending limb of the loop of Henle and the distal convolution appeared to be normal, a pronounced vacuolization of the cytoplasm was found in the ascending limb.

Staining with Sudan III demonstrated that the vacuolization in this section of the nephron was due to fat infiltration of the cytoplasm. Therefore these findings resemble those usually described as lipoid nephrosis.

Because of the general character of our results we feel that the effect of BZ-55 on pancreatectomized dogs may be of significance when the value of this preparation in the treatment of diabetes mellitus is considered.

It must be admitted that the maintenance doses are from four to six times higher than those used in the treatment of diabetic patients and that the findings described above may indicate a specific effect upon the liver and kidneys of animals in which no pancreas is present. It is possible that the damage to the liver cells which impairs the prothrombin synthesis is caused by the lowering of the blood sugar, thereby rendering unsatsifactory conditions for a normal carbohydrate metabolism in both peripheral tissues and liver. It is possible that such conditions also develop in the successfully treated mild, stable, middle-aged diabetics when the pretreatment hyperglycemia is replaced by a much lower blood sugar level over a long period of time.

In one normal dog fed approximately 0.1 gm. BZ-55 per kg. a day the prothrombin value decreased to between 40 and 60 per cent after a month and a half of treatment. No other symptoms appeared which indicated a toxic effect except for a 10 per cent bromsulphalein clearance as compared to the normal 1 to 2 per cent clearance. After five months' continuous treatment the blood counts and the serum proteins were still normal.

THE EFFECT OF D-860

After these studies were completed it became of interest to see if the compound D-860 had a similar effect. A total of three pancreatectomized dogs was used. The daily doses of D-860 and of Insulin Novo Lente are listed in tables 1 and 2 for two of the dogs. In addition, the daily blood sugar concentrations and bromsulphalein clearances are given. The last two columns contain the percentages for the total protein and the albumin content of serum. Evidently the abrupt decrease in prothrombin content is followed by a gradual increase in the bilirubin of the plasma and a decrease in the ability of the liver to remove bromsulphalein after an intravenous injection of 10 mg. per kg. of bodyweight. The effect upon the liver was indicated further by the decrease in the albumin concentration of the serum — in dog no. 32 from 3.6 per cent to 1.6 per cent, in dog no. 30 from 3.7 per cent to 1.8 per cent. At the time of death, a light degree of leucopenia and granulocytopenia was present in both dogs. The third dog, no. 31, showed a similar picture although the course of events was extremely rapid. A dose of 1.5 gm. D-860 daily for three days only caused death four days later, after the last dose. The autopsy revealed no noteworthy findings except for a slight degeneration of the liver and subserous and submucosal hemorrhages. The histological examinations, however, presented evidence of fatty degeneration of the livers of all three dogs, and most pronounced in dogs no. 30 and no. 31. The pathological changes in the kidneys resembled those seen in pancreatectomized dogs fed BZ-55 — an amorphous detritus in the capsular space of some of the glomeruli, vacuolization of the proximal tubules and the ascending limb of Henle's loop. The presence of fat in the vacuolated cytoplasm was also demonstrated in these specimens. Other organs appeared to be normal.

Apparently the mechanism of action of the two compounds is similar and so are the toxic effects observed on the pancreatectomized dogs treated with either BZ-55 or D-860 and insulin simultaneously. After administering orally high doses, 1 to 2 gm. per kg., of D-860 to normal rabbits, Creutzfeldt and Finter[4] observed local dilatations of the most proximal parts of the nephron and protein, or cell, casts in the lumen of Henle's loop and the collecting tubules. These findings were most pronounced in animals dosed for from ten to fifteen days.

Whether these changes can be related to the direct effect of these antidiabetic compounds on either blood sugar or insulin metabolism is unknown at present. However, they may be of interest when related to the indicative results of Cox et al.[5] who found increased amounts of I^{131} insulin in the kidneys of hepatectomized rats treated with D-860. The heavy fatty degeneration in the proximal convoluted tubules of the kidney in pancreatectomized dogs treated with BZ-55 or D-860 supports such an indication of a more specific action of these compounds upon the proximal part of the nephron where also insulin is known to be concentrated.[6] At the same time it must be pointed out that the decrease in prothrombin and albumin syntheses may be the result of a liver damage, as it was not until the last days before death that a low degree of albuminuria was present.

SUMMARY

1. The effect of BZ-55 on the blood-sugar concentrations of pancreatectomized dogs was demonstrated, but it required a simultaneous injection of insulin.

2. Continuous dosing to such diabetic dogs caused a pronounced decrease in the prothrombin value of the blood and the serum albumin concentration. In the final state, icterus developed as well.

3. Hematological studies revealed in some of the cases a slight degree of leucopenia and granulocytopenia.

4. Post mortem, a fatty degeneration of the liver and subserous and submucosal hemorrhages, especially of the gastrointestinal tract, were found. Microscopic examinations confirmed these findings but at the same time demonstrated more pronounced affections in the kidneys. The latter were characterized by a fatty degeneration of the convoluted tubules of the first order and the ascending limb of the loop of Henle, a picture closely resembling the condition classified as lipoid nephrosis. Amorphous, neutrophilic masses sometimes containing nuclei were seen in the capsular space of the renal corpuscle and in the lumen of some of the tubules.

5. Treatment with D-860 caused the same clinical and histological findings characterized by the nephrotoxic and hepatotoxic effects.

6. It is possible that these effects are of special interest for evaluating the safety with which a prolonged therapy with either of the compounds can be established in the stable, middle-aged human diabetic, although we do not know how this condition is related to the diabetes of pancreatectomized dogs.

SUMMARIO IN INTERLINGUA

In Re le Action de BZ-55 e D-860 in Pancreatectomisate Canes

1. Esseva demonstrate le effecto de BZ-55 super le concentrationes de sucro sanguinee in pancreatectomisate canes. In isto le injection simultanee de insulina esseva requirite.

TABLE 1

Dog No. 30—21 kg. pancreatectomized Effect of D-860

Date	8:30 a.m. Insulin Lente i.u.	8:30 a.m. D-860 g.	Blood-sugar at 10 a.m. mg. per cent	Prothrombin* content per cent	Bilirubin mg. per cent	Bromsulphalein† per cent 15′	Bromsulphalein† per cent 30′	Total protein per cent	Albumin per cent
24-8	20	2.5	400	80	0.18			5.8	3.7
25-8	—	—	314						
26-8	—	—	258						
27-8	—	—	186						
28-8	—	—				3.2	2.0		
29-8	—	—	184	13‡	0.20			5.1	3.0
30-8	—	—							
31-8	—	—	326						
1-9	—	—	120						
2-9	—	—	240						
3-9	—	—		52	0.30				
4-9	26	—	264						
5-9	—	—	216						
6-9	—	—	154	48		5.1	5.2		
7-9	—	1.0	122						
8-9	—	—	172						
9-9	—	—							
10-9	—	—		31	0.75	6.9	6.1		
11-9	—	—	112						
12-9	24	—	74						
13-9	20	—	96	10				4.6	1.8
14-9	—	—	80						
15-9	10	—	130						

*10 mg. Bromsulphalein per kg. bodyweight injected intravenously in a 5 per cent solution. The concentrations were determined in the plasma of samples collected fifteen and thirty minutes after the injection.
†Determined by the method of Owren and compared to normal human blood.
‡20 mg. vitamin K injected i.m. daily for the rest of the period.

TABLE 2

Dog No. 32—13 kg. pancreatectomized Effect of D-860

Date	8:30 a.m. Insulin Lente i.u.	8:30 a.m. D-860 g.	Blood-sugar at 10 a.m. mg. per cent	Prothrombin* content per cent	Bilirubin mg. per cent	Bromsulphalein† 15′	Bromsulphalein† 30′	Total protein per cent	Albumin per cent
13-8	14	2.5	365	100					
14-8	—	1.5	285					5.3	3.6
15-8	—	1.0	169						
16-8	—	—	147			2.0	1.5		
17-8	10	—	116	12					
18-8	8	—	190		0.11				
19-8	—	—							
20-8	—	—	274	7		3.5	3.5		
21-8	—	—	322		0.13				
22-8	—	—	270						
23-8	—	—	282						2.8
24-8	—	—	328						
25-8	—	—	350						
26-8	—	—							
27-8	10	—	316						
28-8	—	—	298	4	1.4	6.6	6.2	4.9	2.8
29-8	—	—	292					3.8	1.7
30-8	—	—							
31-8	—	—	212	7	0.9				
1-9	—	—	152			4.0	2.1	3.9	1.6

*10 mg. Bromsulphalein per kg. bodyweight injected intravenously in a 5 per cent solution. The concentrations were determined in the plasma of samples collected fifteen and thirty minutes after the injection.
†Determined by the method of Owren and compared to normal human blood.

2. Le continuate medication de tal canes diabetic causava un reduction marcate in le valor prothrombinic del sanguine e in le concentration albuminic del sero. In le stadio final, il etiam habeva ictero.

3. Studios hematologic revelava in certe casos leve grados de leucopenia e granulocytopenia.

4. Post morte esseva constatate un degeneration grassiose del hepate e hemorrhagias subserosal e submucosal, specialmente in le vias gastrointestinal. Le examine microscopic confirmava iste constatationes e demonstrava simultaneemente plus pronunciate affectiones in le renes. Iste affectiones esseva characterisate per un degeneration grassiose del tubulos convolute del prime ordine e del branca ascendente in le ansa de Henle. Iste tableau esseva multo simile al condition classificate como nephrosis lipoide. Amorphe massas neutrophilic que contineva a vices nucleos esseva vidite in le spatio capsular del corpusculo renal e in le passage de alicunes del tubulos.

5. Le tractamento con D-860 causava le mesme effectos clinic e histologic characterisate per le mesme manifestationes nephrotoxic e hepatotoxic.

6. Il es possibile que iste effectos es de interesse special in evalutar le limites non-riscose de un prolongate therapia con le un o le altere del duo compositos in stabilisate diabeticos human de etates intermediari. Sed il es a notar que nos non sape como iste condition es relationate al diabete de pancreatectomisate canes.

ACKNOWLEDGMENT

The valuable advice and encouragement received from Dr. K. Hallas-Møller, Director of Research, in the course of these studies is gratefully acknowledged. I am indebted to J. Weis-Fogh, M.D., of the Central Laboratory, Copenhagen Municipal Hospital, for the hematological examinations, and to K. E. Sjølin, M.D., for the histological preparations. The skilled technical assistance of Lise Wollesen, Else Bekker and Aase Stricker-Nielsen in the animal testing is highly appreciated.

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Nitrogen Metabolism

The incorporation into proteins of isotopically labeled amino acids was observed to increase after growth hormone administration to intact animals. The rate of protein degradation in similarly treated animals did not change significantly. A significant decrease in the rate of protein breakdown and an increase in amino acid catabolism were observed after hypophysectomy. Growth hormone slowed the rate of amino acid catabolism in hypophysectomized animals, and depressed the rate of urea formation from administered amino acids in nephrectomized rats. Urea formation by liver slices or homogenates from intact adult rats treated with growth hormone was also depressed. No change was observed in the rate of urea formation in the livers of young rats so treated. An interesting consequence of hypophysectomy was the lower loss of nitrogen from diaphragms incubated in vitro. Treatment of the animals with growth hormone restored to normal the rate of nitrogen loss during incubation of the diaphragm.

Sulfur Uptake. The uptake of S^{35} by costal cartilage, presumably into chondroitin sulfuric acid, was decreased by hypophysectomy and was partially restored to normal by growth hormone administration.

From "Enzymatic and Metabolic Adaptations in Animals" by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* *36*:164-254, 1956.

The Toxic Effect of Carbutamide (BZ-55) in Diabetic Dogs

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In a previous report we have described experiments in which prolonged oral administration of carbutamide decreased significantly the daily insulin requirements of one Houssay dog and of one depancreatized dog, while the insulin requirement of another depancreatized dog changed very little.[1] Since then, we have observed that this drug when chronically administered in recommended "maintenance doses" inteferes seriously with the blood clotting mechanism of these adult animals and similar results have been obtained in two depancreatized pups. The blood prothrombin level was markedly decreased in all animals and four of our dogs, out of the series of five, developed fatal hemorrhages.

RESULTS

We first became aware of the possibility that carbutamide could interfere with blood clotting when the Houssay animal after being treated with carbutamide for about thirty-five days (1.0 gm. per day maintenance dose) bled continuously for three days from a venepuncture hole in his radial vein. Repeated transfusions of citrated blood decreased and eventually stopped the bleeding, but the dog was found dead on the following morning. Unfortunately, at that time no arrangements had been made for prothrombin determinations but when the other two adult depancreatized dogs showed similar symptoms, prothrombin levels were measured on the sixty-third day of carbutamide treatment (0.75-1.0 gm. per day maintenance dose) using the prothrombin clotting time method of Quick.[2] The figures are recorded in table 1. It can be seen that the prothrombin levels were low in both of these animals but especially in dog No. 1. This animal was found dead in its cage on the next morning, but dog No. 2 survived.

In order to extend our observations, two litter mate puppies were surgically depancreatized at the age of four and one-half months when their weights were 3.2 and 5.0 kg. respectively. The diabetic puppies were stabilized on regular (Toronto) and Protamine Zinc insulin for three months before administration of carbutamide *per os* was commenced. The experiment was designed in the same fashion as described in the previous paper[1] and determinations of prothrombin clotting times were included.[2]

TABLE 1

Prothrombin clotting times of normal, depancreatized and depancreatized-BZ-55 treated dogs.

Animal	Days on BZ-55	Prothrombin time (sec.) FS[x]	50%	25%	12.5%
Normal puppy	—	14	11	15	21
Normal adult dog	—	10	9	14	19
depancr. puppy	—	9	9	16	33
depancr. adult dog	—	9	9	13	20
depancr. puppy No. 1	39	48	120	280	>300
depancr. puppy No. 2	39	14	17	23	47
depancr. adult dog No. 1	63	62	78	158	>300
depancr. adult dog No. 2	63	15	18	20	36

[x] F.S.: Full strength oxalated plasma. Blood withdrawn into one-tenth its volume of 0.1M sodium oxalate.

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The blood and urine sugar values with twenty-four hour urine volumes, the daily insulin requirements, and the dose and blood level of carbutamide are given for each diabetic puppy in figure 1 and 2. At first it seemed that the two depancreatized puppies would not respond to carbutamide in the same fashion. While the insulin requirement of No. 1 did not seem to change, No. 2 responded favorably and the insulin dose was halved in the second week of carbutamide treatment. Later on, however, it was impossible to keep this dog well controlled and the insulin doses had to be increased substantially.

On the thirty-seventh day of carbutamide treatment puppy No. 1 ate only part of his ration. The next day he would not eat any of his regular diet* or of another more attractive one. Vomiting occurred. On the thirty-ninth day blood samples were taken for prothrombin determinations and for routine estimations of glucose and sulfonamides in blood. As shown in table 1, the prothrombin values were low for both puppies. No. 1 was found dead in its cage on the following morning. No. 2 died on the forty-second day of carbutamide administration. The latter animal appeared healthy and ate very well until the last day before death.

The post-mortem examination of our four diabetic animals revealed subendocardial petechiae in two animals and severe hemorrhages in the abdominal viscera in three animals. There was no evidence of brain hemorrhages. The common finding in all four animals was that of an enlarged liver. In the pups huge yellow livers, friable in consistency, were the most striking findings. The animals died during the night and at autopsy in the morning it was impossible to determine the immediate cause of death. The post-mortem changes made conclusions from the histological findings very difficult. There was little doubt, however, that the accumulation of fat in the liver was beyond physiological limits. There was suggestive evidence, which awaits confirmation, that the glycogen stores in the liver were also increased.

*Measured amount of commercial dog food supplemented with raw pancreas.

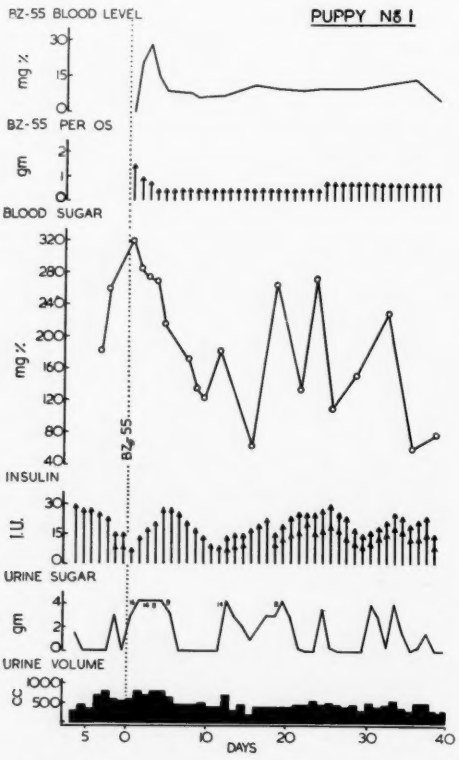

FIG. 1. BZ-55 had no remarkable effect on blood sugar and insulin requirement.

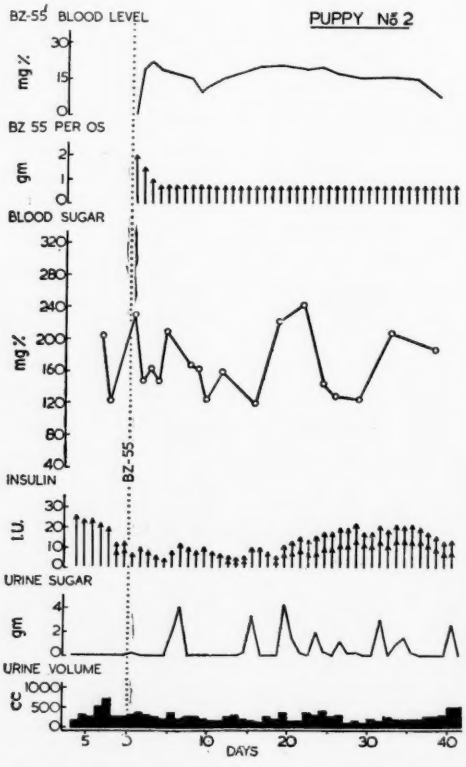

FIG. 2. BZ-55 had no remarkable effect on blood sugar and insulin requirement.

DISCUSSION

It is unlikely that malnutrition played a part in the fatal outcome of these experiments. The adult dogs were not losing weight and the puppies kept growing and were well developed. Toxic effects must then be considered as the causative factor. The drug was carefully administered in the recommended amounts and at no time did the blood levels rise above those reported as safe by the German authors.[3, 4, 5] When our experiments were terminated we learned that Dr. Schambye from the laboratory of Professor Hallas-Møller in Denmark also found bleeding tendencies and fatty livers in depancreatized adult dogs treated with carbutamide.[6]

SUMMARY

Four of five depancreatized dogs given carbutamide for prolonged periods in the amounts recommended for human patients developed eventually fatal hemorrhages.

SUMMARIO IN INTERLINGUA

Le Effecto Toxic de Carbutamido (BZ-55) in Canes Diabetic

Quatro ex cinque dispancreatisate canes, habente recipite carbutamido durante prolongate periodos de tempore in le dosage recommendate pro patientes human, disveloppava extense e finalmente mortal hemorrhagias.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Professor F. C. Monkhouse for the determinations of the prothrombin clotting times and to Professors W. G. B. Casselman and H. J. Barrie for preparing and evaluating the histological sections.

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Enzymatic and Metabolic Adaptations in Animals

A few correlations between enzyme levels and function can be made at present in diabetic animals. The level of blood sugar, which is formed by the action of liver glucose-6-phosphatase, can be correlated with the level of this liver enzyme in certain physiological states. For example, the activity of this enzyme is elevated in diabetic animals. It is of particular interest, therefore, that adrenalectomy of normal animals did not change this enzyme activity, but that adrenalectomy of diabetic animals decreased the high enzyme level characteristic of diabetes. The difference in response of this enzyme to adrenalectomy in normal and diabetic animals shows the importance of the metabolic state of the cell in determining the response of an enzyme to a given stimulus. More important is the fact that the decrease in glucose-6-phosphatase of diabetic animals produced by adrenalectomy is consistent with the general amelioration of the diabetes by adrenalectomy which was first described by Long and Lukens. Since abnormalities of protein catabolism characteristic of diabetes were also substantially reversed by adrenalectomy of the diabetic animals, it might be predicted that enzymes concerned with protein catabolism which were altered in diabetes would also be restored toward normal levels by adrenalectomy. The only enzyme of this sort studied in diabetes is transaminase, but no studies of this enzyme in adrenalectomized-diabetic animals have been reported. Reasoning from the correlations of changes in enzyme levels with physiological functions found after thyroid treatment, it might be expected that still other disturbances in diabetes might be referable to changes in the levels of a number of other enzymes.

From the article by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* 36:164-254, 1956.

Studies of Sodium Diethyldithiocarbamate, A Supposed Pancreatic Alpha Cell Toxin

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It has been reported that certain organic compounds capable of combining with zinc in pancreatic islet tissue are able to induce a permanent hyperglycemia.[1] Similar to the results following alloxan administration, the blood sugar curve produced is characterized by a triphasic cycle: initial hyperglycemia, subsequent hypoglycemia, and a final, permanent hyperglycemia. It was further reported,[2] that one of these organic agents, sodium diethyldithiocarbamate (hereafter referred to as NaDDC), though producing a hyperglycemia with subsequent return to normal in eleven out of fifteen animals tested, yielded in the remaining animals, during the time interval studied, a permanent hypoglycemia which was refractory to intravenous glucose therapy. This permanent hypoglycemia was correlated with degenerative changes in the alpha cells of the pancreatic islets. In addition, it has been reported that NaDDC is capable of returning the blood sugars of obese hyperglycemic mice to normal for extended periods of time.[3]

In light of the above considerations, and in view of the speculated role of the alpha cell as a source of a hyperglycemic - glycogenolytic factor,[4, 5, 6, 7, 8] further study of the reagent sodium diethyldithiocarbamate seemed warranted. The purpose of the present studies is to correlate the observed blood sugar changes following administration of NaDDC with possible alterations in the pancreatic islets, and to attempt to gain further insight into the mechanism of these changes.

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METHODS AND MATERIALS

Sodium diethyldithiocarbamate was administered intravenously and intraperitoneally in the rabbit (earlier studies indicating no difference in blood glucose responses or pathological changes via these two routes of administration), and intraperitoneally in the rat, in the form of an isotonic saline solution-suspension, in single rapid doses ranging from 0.5 to 1.2 gm./kg. Young, healthy, virgin female rabbits, and young, healthy white male rats, averaging 2 kg. and 250 gm. respectively, were used as experimental animals. Adrenalectomies in rats were performed as two-step procedures under light ether anesthesia. An interval of three to five days was allowed after removal of the first adrenal gland for recovery, followed by extirpation of the second gland, and prompt institution of the experimental procedure. Animals serving as controls were subjected to identical operative procedures, with substitution of isotonic saline in place of the experimental drug. In all cases of unilateral or bilateral adrenalectomy, the only supportive therapy was 1 per cent saline as drinking water in addition to a standard balanced laboratory feed. Blood glucose was determined by the macromethod and micromethod of Folin-Wu[9] and Folin-Malmros,[10] respectively. Capillary blood from the rat's tail, and venous blood from the rabbit's marginal ear vein were used routinely for glucose analysis. In the adrenalectomized series, the final sample was frequently taken by cardiac puncture.

Specimens of tissue were removed within one minute following death. Pancreatic tissue was fixed in Bouin's solution, cut at 4μ, and stained using Gomori's chrome alum hematoxylin-phloxin method.[11, 12] In all cases, control slides cut from a fresh block of normal pancreatic tissue were run with each group of experimental slides to evaluate variations in fixation and staining. Histologic sections of pancreas, liver, and kidney stained with hematoxylin and eosin were routinely examined.

RESULTS

Twenty-four rabbits of Series 1 received 0.5 to 1.0

gm./kg. of NaDDC. Fifteen of these animals were permitted to survive in an attempt to observe the full cycle of blood glucose changes, as indicated in figure 1. With the exception of one animal that died in initial hypoglycemia, the remaining were sacrificed (twelve animals), or died (two animals) well after the blood glucose levels had stabilized. The remaining nine animals were sacrificed at particular points in the blood glucose cycle to provide tissue corresponding to these levels. The findings may be summarized as follows:

Series 1	*No. of Animals*
Initial hyperglycemia with return to normoglycemic range	11
Initial hypoglycemia and death	1
Initial hyperglycemia, subsequent hypoglycemia, and return to normoglycemic range	2
Initial hyperglycemia, subsequent hypoglycemia, and fluctuating hyperglycemia	1
Total	15

It may be seen, that with the exception of one animal (initial hypoglycemia and death), all animals exhibited an initial hyperglycemia. Thirteen out of the fifteen animals subsequently returned and stabilized at normoglycemic levels. Although the possibility of a transient hypoglycemia occurring during the eight- to twenty-hour period exists, no convulsions or deaths were noted during that interval.

A group of ten rabbits received the drug in doses of 1.1 to 1.5 gm./kg. At this dosage level, NaDDC was found to be markedly toxic, all animals dying within the first hour, several within minutes of injection. Blood glucose and tissue studies were not done.

Series 2 consisted of sixteen rats that received 0.7 to 1.0 gm./kg. of NaDDC. The time and results of blood glucose analysis are tabulated in figure 2. The results may be summarized as follows:

	Number of Animals
Initial hyperglycemia with return to normoglycemic range	10
Unaffected	6
Total	16

It may be seen, therefore, that the dose of NaDDC capable of regularly producing an initial hyperglycemia in rabbits was capable of producing a similar response in only ten of sixteen rats tested. No animals manifested a subsequent hypoglycemia with this dose.

In Series 3 rats received doses of NaDDC from 1.1 to 1.2 gm./kg. An attempt was made in ten animals to allow the blood glucose response to run its full course. Several additional animals were sacrificed to provide tissue during the initial hyperglycemic phase. The results, figure 3, may be summarized as follows:

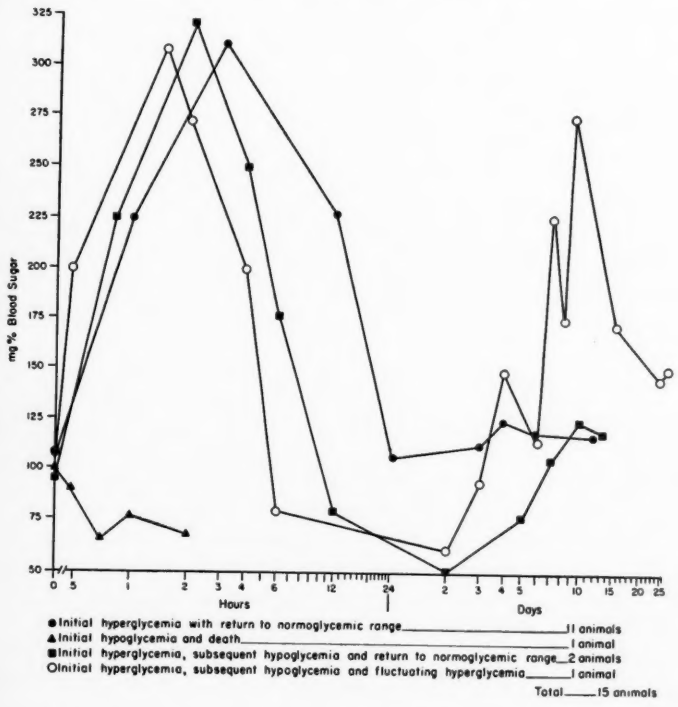

FIG. 1. The effect of sodium diethyldithiocarbamate on the blood glucose of fifteen rabbits when administered in doses of 0.5-1.0 gm./kg. intravenously and intraperitoneally.

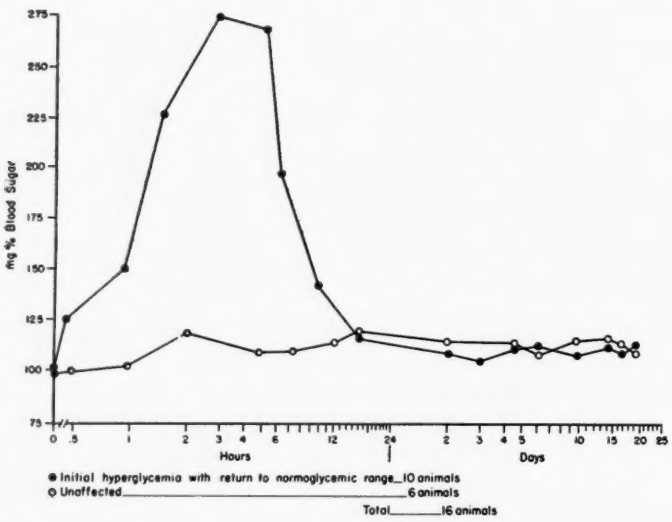

FIG. 2. The effect of sodium diethyldithiocarbamate on the blood glucose of ten rats when administered in doses of 0.7-1.0 gm./kg. intraperitoneally.

	Number of Animals
Initial hyperglycemia, subsequent hypoglycemia and death	5
Initial hyperglycemia and death	1
Initial hyperglycemia, return to normoglycemic range, and death	3
Initial hyperglycemia, subsequent hypoglycemia and return to normoglycemic range	1
Total	10

It may be seen, therefore, that with increased doses of NaDDC, nine out of ten animals exhibited an initial hyperglycemia, with death probably occurring on the way toward hypoglycemic levels.

Series 4 consisted of twelve bilaterally adrenalectomized rats that received 0.7 to 1.0 gm./kg. of NaDDC. Results are portrayed in figure 4 and may be summarized as follows:

	Number of Animals
Initial hyperglycemia	0
Initial hypoglycemia and death	12
Total	12

During the three to four hours following removal of the second adrenal gland and injection of NaDDC, the animals became increasingly moribund, and died. Blood glucose determinations of saline control animals remained within normal limits, as indicated in figure 4. They did well, and were sacrificed on the fourth and eleventh days. All test animals failed to exhibit any hyperglycemic response. The overall effect was a relatively rapid developing hypoglycemia and death.

PATHOLOGY

On the basis of rigid evaluation of the experimental sections with respect to the control slides, we were unable to demonstrate any pathological changes in either the rabbit or rat pancreatic sections, intact or adrenalectomized, taken in all stages of blood glucose variation following the administration of NaDDC.

An exception to this statement was an animal from Series 1 which passed through a cyclic response, characterized by initial hyperglycemia, subsequent hypoglycemia, and a final state, which fluctuated between high normal and distinct hyperglycemia over a period of nineteen days, until sacrificed. Pancreatic islet changes in this case showed a moderate and consistent beta cell necrosis throughout the sections, similar to Kadota's dithizone diabetes.[1] Routine hematoxylin-eosin staining of liver and kidney sections disclosed no significant histological alteration.

DISCUSSION

Considerable insight into the nature of the initial hyperglycemia of alloxan diabetes was gained quite early in alloxan investigations, with evidence pointing to a direct glycogenolytic effect on the liver,[14, 15] a response mediated via the adrenal medulla,[16, 17] and through an adrenal pituitary mechanism.[18] In the light of histochemical studies, Kadota[1] speculated that the initial hyperglycemia produced by his organic zinc-precipitating reagents was due to an instantaneous combination of these reagents with zinc in the pancreatic islets. The

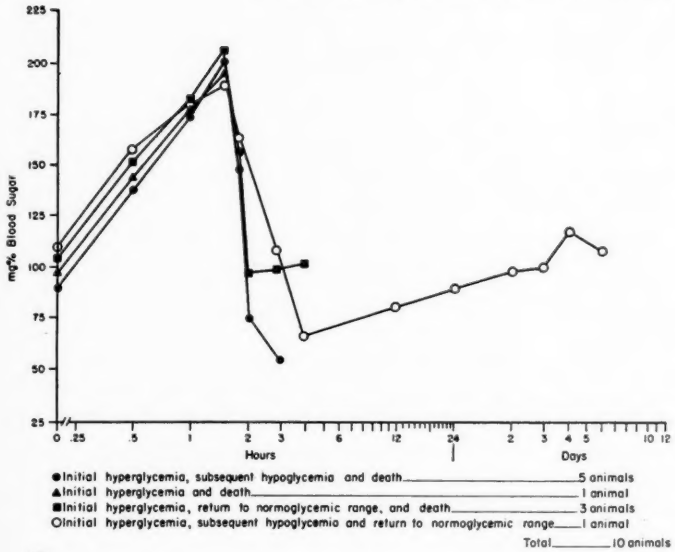

FIG. 3. The effect of sodium diethyldithiocarbamate on the blood glucose of ten rats when administered in doses of 1.1-1.2 gm./kg. intraperitoneally.

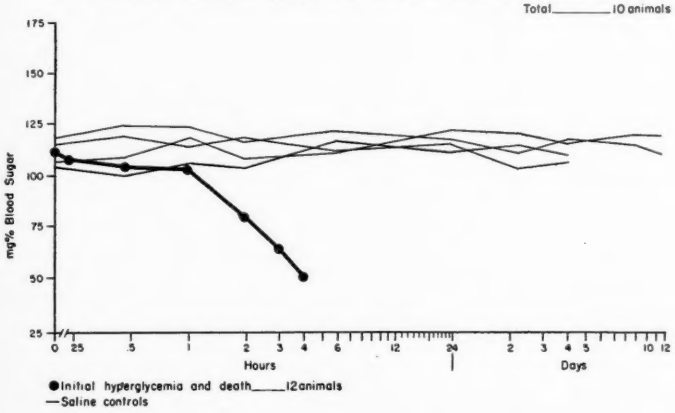

FIG. 4. The effect of sodium diethyldithiocarbamate on the blood glucose of twelve adrenalectomized rats when administered in doses of 0.7-1.0 gm./kg. intraperitoneally, and also the response of four adrenalectomized saline control animals.

mechanism for the production of the initial hyperglycemia following the administration of NaDDC, a known zinc precipitating reagent, is apparently not analogous to the proposed mechanism for the initial hyperglycemia using dithizone or oxine as the reagent. (It might be mentioned at this point that our unpublished data verify the blood glucose alterations of Kadota's dithizone diabetes during a smaller time interval studied). Rats deprived of their adrenals consistently failed to show the initial hyperglycemia seen in the intact animals which had received similar doses. These adrenalectomized animals invariably died within three to four hours, several in severe hypoglycemia. Evidence that this initial hyperglycemia depends for the most part on an extrapancreatic basis is further augmented by the failure to find any pancreatic islet pathology in animals either sacrificed or dying over the full range of initial hyperglycemia and hypoglycemia following administration of NaDDC.

It may be concluded, therefore, that the initial hyperglycemic response following administration of NaDDC requires the integrity of the adrenal gland, and cannot be fully explained, if at all, on the basis of alteration in pancreatic physiology.

Furthermore, though the alpha cell has been implicated in explaining the hypoglycemic response to NaDDC,[2] no histological evidence of alpha cell alteration was seen in this study which could be considered to be significant. In view of the fact that it was impossible to induce a sustained hypoglycemia with doses of NaDDC compatible with life, or alpha cell destruction within the dose range of NaDDC studied, and considering the ease with which alpha cell damage has been reported after cobalt administration,[19] or Synthalin A,[20] use of NaDDC for this purpose does not seem warranted. A re-evaluation of

those studies performed since the introduction of NaDDC as an alpha cell toxin, which depended on this specific action of the drug, would also appear to be indicated.

SUMMARY

1. The response of rabbits to doses of 0.5 to 1.0 gm./kg. of sodium diethyldithiocarbamate intravenously and intraperitoneally administered, and the response of rats to doses of 0.5 to 1.0 gm./kg. of this drug intraperitoneally administered is one of initial hyperglycemia with return to normal range in the majority of animals tested. Triphasic blood glucose curves of the alloxan type were only occasionally encountered, as was the development of permanent hyperglycemia (one animal).

2. Doses above 1 gm./kg. were found to be fatal to both rabbits and rats.

3. Inasmuch as histological studies of rat and rabbit pancreatic tissue following administration of 0.7-1.0 gm./kg. of sodium diethyldithiocarbamate failed to show any consistent pathological change, and noting that adrenalectomized rats failed to manifest a hyperglycemic response with a similar dose, it is concluded that the hyperglycemia following injection of the above reagent is essentially extrapancreatic in nature, and requires the integrity of the adrenal gland.

4. Use of sodium diethyldithiocarbamate as a pancreatic alpha cell toxin is seriously questioned.

SUMMARIO IN INTERLINGUA

Studios de Diethyldithiocarbamato de Natrium

1. Le responsa de conilios a doses de 0,5 a 1,0 g per kg de diethyldithiocarbamato de natrium in administrationes intravenose e intraperitoneal e le responsa de rattos a doses de 0,5 a 1,0 g per kg del mesme droga in administrationes intraperitoneal consisteva de hyperglycemia initial sequite per un retorno a valores normal in le majoritate del animales studiate. Triphasic curvas de glucosa sanguinee, del typo de alloxano, esseva trovate non plus que sporadicamente, e le disveloppamento de hyperglycemia permanente non occurreva in plus que un sol caso.

2. Doses de plus que 1 g per kg se provava letal pro conilios e pro rattos.

3. Viste que studios histologic de tessuto pancreatic de rattos e conilios post le administration de 0,7 a 1,0 g per kg de diethyldithiocarbamato de natrium non revelava ulle uniforme alteration pathologic e viste que rattos adrenalectomisate non reageva per un responsa hyperglycemic a simile doses, on debe concluder que le hyperglycemia que occurre post injectiones del agente mentionate es de character essentialmente extrapancreatic e require le integritate del gandula adrenal.

4. Le uso de diethyldithiocarbamato de natrium como toxina a cellulas pancreatic alpha es a considerar como seriemente questionabile.

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The Vascular Complications of Diabetes Mellitus

A Clinical Study

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The most important consequences of diabetes mellitus today are vascular complications. Recession of diabetic coma and of infection as causes of death since the discovery of insulin and the wide clinical use of antibiotics is well known and has increased life expectancy. The prolongation of diabetic lives based on studies of fatal cases is indicated by Joslin's[1] results showing the increased average duration of life after the onset of diabetes from 6.1 years before 1922 to 15.6 years as of Dec. 1, 1955.[2] Before insulin the average duration of life with onset of diabetes below age twenty was under three years and now exceeds twenty years,[2] more than a six-fold increase in life expectancy for the younger diabetic subject. With this greater prolongation of life vascular complications have become increasingly important.

Post-mortem studies[3, 4, 5] bear out the importance of vascular lesions as a cause of death. In Bell's series[5] of 1,559 autopsies performed on diabetic persons between 1910 and 1951, vascular disease was causative or a major factor contributing to death in 49.3 per cent of the cases, in contrast to 24.5 per cent for nondiabetic persons. The high incidence of vascular deaths in cases of diabetes was due "chiefly to a greater frequency of gangrene, coronary disease and renal arteriosclerosis."

That vascular disease has gained increased eminence as a cause of death is reflected in an analysis of over 10,000 diabetic deaths subsequent to 1898.[6] Thus, before 1914, the cause of death was cardiorenal vascular in 17.5 per cent. In 1922 the figure was 24.6 per cent; in 1936, 54.2 per cent; in 1949, 70 per cent, and by 1955, 76 per cent. The trend among juvenile diabetic patients is no less striking, especially with respect to the incidence of renal disease. Of forty-nine juvenile patients (onset of diabetes 15.0 years or less) who died before 1930, nephropathy was listed as the cause of death in two and heart disease in one. Of 160 similar cases between 1947 and 1951, nephropathy was the cause of death in seventy and heart disease in twenty-nine.[7] Among 201 juvenile diabetics who died between 1950 and December 1955, renal disease accounted for 153 deaths and heart disease for twenty-eight.[2]

Reports of vascular complications in living diabetic patients are less common. Martensson[8] studied 221 diabetic persons surviving at least fifteen years and reported evidence of coronary arteriosclerosis in 43 per cent; gangrene, chronic ulcerative lesions of the feet or severe arterial insufficiency in 19 per cent; and nephropathy in 34 per cent. White and Waskow[9a] studied 200 patients with juvenile diabetes who survived twenty years and found evidence of vascular disease in 92 per cent.

White[9b] has recently reported a progressively increased incidence of vascular complications among 1,072 juvenile diabetics surviving twenty years or more after the onset of diabetes. "At 35 years' duration nearly all showed lesions; 94 per cent had calcified arteries, 93 per cent retinopathy, 59 per cent neovascularization, 53 per cent hypertension, 44 per cent nephropathy. These lesions were not observed in the first five years of diabetes, rarely found in the first ten years, but by fifteen years, 19 per cent of those examined had retinopathy, 14 per cent calcified arteries, 7 per cent proteinuria, 4.5 per cent hypertension, 3 per cent proliferans . . ."

The incidence of arteriosclerotic heart disease in living diabetic patients was studied by Liebow, Hellerstein and Miller[10] in 383 diabetic outpatients, all of whom were over forty years of age. They found 42 per cent with clinical arteriosclerotic heart disease, although a considerably smaller percentage had angina or myocardial infarction. The latter findings, according to Harrison[11] should be present for the clinical diagnosis of arteriosclerotic heart disease.

Brandman and Redisch[12] have recently studied the incidence of peripheral vascular changes in diabetics. "Relative peripheral arterial insufficiency" (postural color changes or an absent pulsation in at least one foot) was found in 30 per cent within five years and in over 52

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per cent by fifteen years after the onset of diabetes. However, in all cases with duration of ten years or more, the patients were above age thirty at onset of diabetes.

Wagener,[13] who has considered the small vascular lesions of the eye the earliest and the most characteristically diagnostic vascular lesion of diabetes, reported an increasing incidence of diabetic retinopathy in his series; in 1921 the incidence was 8.3 per cent; in 1934, 17.7 per cent; and in 1945, 30.6 per cent.

Data relative to the incidence of intercapillary glomerulosclerosis are confined for the most part to the post-mortem studies in which the lesions have been observed in from 15 to 64 per cent of cases.[14, 15, 16, 17, 18] In a group of 247 young living patients with diabetes of long duration sixty-two, or 25 per cent, were found to have diabetic nephropathy[19a] which the authors point out represents a mixed lesion. The precise clinical diagnosis of intercapillary glomerulosclerosis may be difficult. Bell[18] has observed that the lesion may be present post-mortem, when previously proteinuria was mild or even absent clinically.

The outstanding study of Wilson, Root and Marble[19b] demonstrated that control of the disease, as well as its duration, influenced the incidence and severity of retinitis, nephropathy and the X-ray finding of calcified arteries.

This was a selected group in that all subjects were young (thirty years or less) at onset of diabetes, which endured from ten to thirty-four years. The prevalence of vascular lesions in their series is obviously not comparable to that in the present study, but the striking finding was essentially one-half as much vascular disease in the controlled diabetic as compared to those who were poorly controlled. This was true for all durations of diabetes after ten years.

The above representative studies reflect the incidence of the various complications considered either singly or as they occurred together in specially selected groups of diabetic patients.

Because of this and the changing incidence of vascular complications, there appeared to be a need to reassess the problem in the living diabetic today. This, it seemed, would be best accomplished by evaluating a large group of unselected diabetics for the presence of the principal vascular complications. Accordingly, 394 diabetic admissions to the New England Deaconess Hospital were observed at random for the presence of any of the following: (a) diabetic retinopathy, (b) diabetic nephropathy, (c) vascular foot lesions, and (d) arteriosclerotic heart disease.

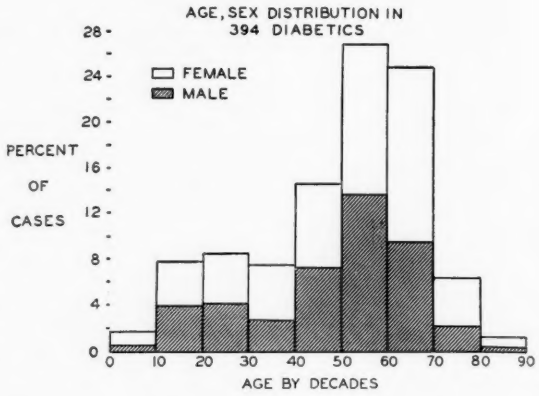

FIGURE 1

CLINICAL MATERIAL AND METHODS

The manner of selection of cases was as follows: For successive periods of from four to six weeks, all admissions to certain divisions of the diabetic service of the New England Deaconess Hospital were especially studied for the presence of the complications noted above. In this manner cases from all social and economic levels were included. Patients with diabetes of relatively short duration were included so that the incidence and extent of the vascular changes in this group, in whom one would not ordinarily expect a great incidence of vascular degenerative changes, could be compared with the incidence in those of long duration.

The age and sex distribution is indicated in figure 1 and the duration of diabetes in figure 2. There was an equal number of males and females of younger age (below thirty), while there were more females in the older decades, especially the seventh and eighth. Thus, the sex distribution in these groups is that which has been observed in the diabetic population at large.

Evaluation included a complete history and physical examination, chest X ray and electrocardiogram, and pertinent urine and blood chemical studies. The following criteria were applied for the diagnosis of the various complications.

Diabetic retinitis. The ocular fundi were examined in a darkened area without the aid of a mydriatic. The changes observed were graded according to the criteria used previously by Keiding and co-workers:[20] Grade I—few scattered microaneurysms or punctate hemorrhages in one or both retina, with no exudates; grade II—several microaneurysms or petechial hemorrhages in both fundi and a few to many small hard and/or soft white exudates bilaterally; grade III—multiple scattered micro-

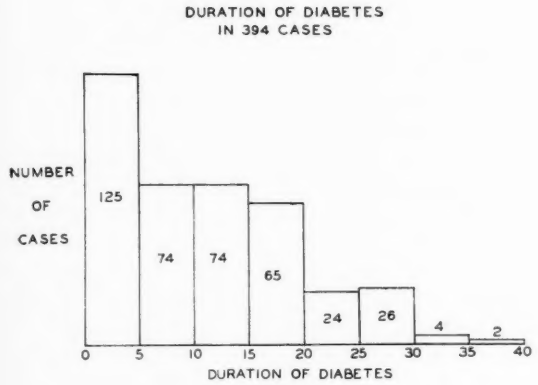

FIGURE 2

aneurysms or hemorrhages bilaterally, some splinter hemorrhages and many exudates scattered about both retinas; grade IV—severe advanced retinitis with large hemorrhages and/or proliferative changes (retinitis proliferans), retinal detachment and acute or chronic hemorrhagic glaucoma. In only exceptional cases with opaque media (cataracts) or very small miotic pupils was it impossible to obtain a view of the fundus; the number of these cases is indicated in the results.

Diabetic nephropathy. The precise diagnosis of intercapillary glomerulosclerosis requires histologic examination and more often than not, especially in younger patients, the renal picture will be one of a mixed lesion including pyelonephritis and arteriolar sclerosis.[18, 19a] The term nephropathy, rather than intercapillary glomerulosclerosis, has, therefore, been used here. The presence of persistent albuminuria greater than 60 mg. per cent, when not obviously due to other causes, was considered as presumptive evidence of diabetic nephropathy. Nitrogen retention was considered to be present when the blood nonprotein nitrogen level exceeded 40 mg. per cent.

Peripheral vascular complications. The complications considered here were those evidenced by visible lesions or intermittent claudication; those lesions secondary to neuropathic changes or to varicose veins and stasis or due to infection occurring in the presence of what was clinically considered to be adequate peripheral circulation, were excluded from analysis in this study.

Arteriosclerotic heart disease. The criteria for the presence of arteriosclerotic heart disease were those set forth by the New York Heart Association.[21] Thus, the diagnosis rested upon the "findings of symptoms or abnormal physical signs indicating (a) arteriosclerosis of the coronary arteries; (b) thrombosis or occlusion of one or more coronary branches, (c) fibrosis of the myocardium, (d) sclerosis of a valve, and (e) arteriosclerosis of the aorta." Detailed information was assembled relative to angina and myocardial infarction. In addition to these cases with definite clinical heart disease and symptoms, cases with abnormal electrocardiograms, calcified aorta or cardiomegalia occurring in the absence of hypertension and in whom the diagnosis of arteriosclerotic heart disease seemed likely were considered separately. Hypertension was considered present if the systolic or diastolic blood pressure persistently exceeded a level of 150/90.

RESULTS

Of the 394 cases studied, definite evidence of vascular disease was present in 195, representing a total incidence of 49.5 per cent, considered irrespective of age and duration of diabetes. If those with electrocardiographic and other changes suggesting coronary arteriosclerosis are considered, the number increases to 239 and the incidence to approximately 61 per cent. The tendency for vascular changes to be diffuse is indicated by the presence of multiple lesions in 47.3 per cent, or almost one-half, of all patients in whom any vascular degenerative disease was present.

The effect of duration of diabetes is apparent from an inspection of figure 3, in which is illustrated the incidence as well as the relative preponderance of the various complications in groups of individuals arranged according to the duration of diabetes. In those with diabetes of less than five years' duration, 19.2 per cent presented evidence of definite vascular disease. After five to ten years of diabetes the incidence was 33.8 per cent; after ten to fifteen years, 59.4 per cent; after fifteen to twenty years, 81.6 per cent and after twenty

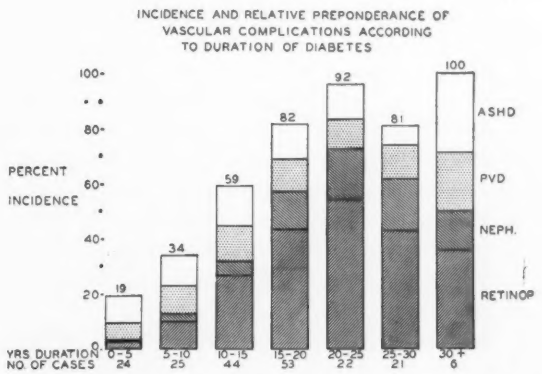

FIG. 3. ASHD, arteriosclerotic heart disease; PVD, peripheral vascular disease; NEPH, nephropathy; RETINOP, retinopathy.

years or more, 87.5 per cent. At thirty years' duration or more, all of the six diabetics showed at least one vascular lesion. Thus, the incidence of vascular complications in those with diabetes of twenty or more years' duration does not differ greatly from the figure of 92 per cent given by White and Waskow[9] for juvenile diabetic patients surviving twenty years or more after the onset of diabetes.

The occurrence of vascular degenerative disease in 24 of 125 cases (19.2 per cent) with diabetes of less than five years' duration is somewhat unexpected. In twenty of twenty-four cases, however, the condition present was a result of atherosclerotic changes (arteriosclerotic heart disease and/or peripheral vascular disease), which are not specific for diabetes. In 3 cases, retinal changes were observed and in one there was retinopathy and nephropathy. In none of these four cases, however, was there certainty as to the duration of diabetes. In contrast to this group with diabetes of less than five years' duration and in whom atherosclerotic complications predominated are the fifty-three cases with diabetes of from fifteen to twenty years, in whom one or more vascular complications existed. This group, as figure 3 reflects, is representative of those with diabetes of many years' duration. In forty-five, or 83 per cent, diabetic retinopathy existed, and in fourteen, or 26 per cent, nephropathy was present. Arteriosclerotic heart disease was present in thirteen, or 25 per cent, and peripheral vascular disease was observed in twelve, or 23 per cent. In this group, then, atherosclerotic complications were less prevalent than the retinal and renal lesions so characteristic of long-standing diabetes.

Detailed consideration is given below to the various complications which were present in the frequency noted in figure 4.

Diabetic retinitis. It was possible to examine the ocular fundi in 370 of the 394 cases studied, of whom 141 had definite eyeground changes. This represents an incidence of 38.1 per cent in those cases examined and 35.8 per cent of all cases. Retinitis appeared in 3.3 per cent of those having diabetes for zero to five years and increased to over 85 per cent in patients having diabetes for twenty-five years or more. The greatest increments in retinitis were found at ten to fifteen years (51.4 per cent) and at fifteen to twenty years (77.6 per cent).

The 141 patients with retinitis were divided according to severity (figure 4). Average age in grades I through IV were 49, 55, 56 and 46 years. Diabetes had been present for sixteen years in those having grade I retinitis, and increasing severity of retinitis

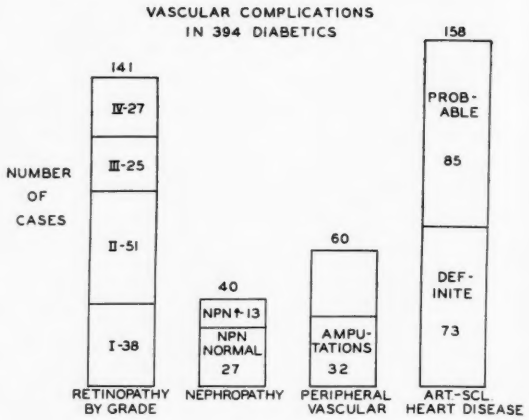

FIGURE 4

was associated with a longer duration of diabetes for each grade, reaching 19.3 years in those having Grade IV findings. The latter group had developed diabetes at a younger age but had longer durations of the disease than did those with milder grades of retinal change.

Over one-half of the cases with the most advanced eyeground findings had albuminuria, which was found in only eleven of the eighty-nine diabetics with grade I and II retinal changes. The association of eyeground changes and diabetic nephropathy is well known and constitutes part of the evidence in favor of the concept that the two lesions may be fundamentally related.[22, 23, 24]

There were four cases of retinitis in the series in whom the duration of diabetes was given as being less than five years. One of these individuals also had nephropathy. Wagener[13] has noted the occasional occurrence of retinopathy in persons having no evidence of clinical diabetes other than a positive glucose tolerance curve. Careful analysis of the four cases here indicates that the durations of diabetes could not be accurately assessed and that in all probability the diabetes was long unrecognized and, furthermore, long uncontrolled. All too often diabetic retinopathy is the initial finding leading to the diagnosis of diabetes. The high incidence of retinal changes, especially in those with diabetes of long standing, is tempered somewhat by the fact that a great many of those with lesser changes were asymptomatic and had suffered little loss in visual acuity.

Diabetic nephropathy. Findings indicated the presence of diabetic nephropathy in forty cases (figure 4), an over-all incidence of approximately 10 per cent. The incidence in 195 cases with diabetes of ten or more years' duration was 18.5 per cent and was 24 per cent

in 121 cases with diabetes for fifteen or more years. The latter figure compares with one of 34 per cent given by Martensson,[8] who studied 221 live diabetics who had survived at least fifteen years.

Of the forty diabetic cases with nephropathy there were twenty-two females and eighteen males. The prevalence in females was less striking than that reported in autopsy studies.[15, 18] The average duration of diabetes was 18.8 years.

There were eleven juvenile diabetic cases. That nephropathy is more characteristic of the younger diabetic, is now well-recognized, in contrast to the early reports wherein intercapillary glomerulosclerosis was observed in older individuals.

Several authors[18, 25] have indicated that the classical clinical manifestations of hypertension, abuminuria and edema may be absent in cases proved pathologically to demonstrate lesions of intercapillary glomerulosclerosis. In this study persistent hypertension was not present in seven of forty cases, including two with an elevated nonprotein nitrogen. Albuminuria was present in all cases, and in general the presence or absence of edema varied with the severity of the albuminuria, which ranged up to 670 mg. per cent.

The average daily insulin dose for those with nephropathy was slightly higher than the average dose for all the diabetics in this series, the figures being 36 and 34 units respectively. However, the average dose in those with uremia was 28, while in those without uremia it was 41 units. Changes in insulin requirements and the diabetic state in cases of intercapillary glomerulosclerosis have been noted by several authors.[26, 27] The data in this limited number of cases are not sufficiently conclusive to warrant a statement regarding the effect of advanced renal disease on insulin needs.

Definite eyeground changes were present in all thirty-six patients with nephropathy whose fundi could be examined; in seventeen patients the changes were of the most advanced grade, and in only three were the changes noted to be minimal. Thus, while nephropathy was always accompanied by retinopathy, the converse did not always apply. Friedenwald,[22, 23, 28] who has studied the association of retinal microaneurysms and renal changes, suggests that the typical globular, hyaline, glomerular nodule of intercapillary glomerulosclerosis may be a hyalinized saccular capillary aneurysm. Ashton[29] has held somewhat similar views and believes that intercapillary glomerulosclerosis and retinopathy are manifestations of the same pathologic process modified by the different anatomic structure of the retinal and glomerular vessels. From careful post-mortem studies of the retina, he concluded that the renal lesions of diabetes are always accompanied by retinal microaneurysms or other retinal changes, whether they are detectable clinically or not. Our findings also indicate that the retinal lesions are more easily detectable at an early asymptomatic stage.

Peripheral vascular complications. Sixty-two cases (thirty-three female and twenty-nine male), or 15.7 per cent of all cases, presented evidence of frank, clinical peripheral vascular insufficiency. Of these cases, thirty-two had undergone at least a partial amputation. The average age of the patients and the duration of diabetes in those with this complication was 62.2 and 13.0 years respectively, and the average daily insulin dose was 31 units. Twenty-three patients, or 37 per cent, were more than 5 per cent over the average weight for individuals of the same age,[30] as compared with approximately 34 per cent of all cases, so that there was no significant correlation between obesity and peripheral vascular disease.

That senescence or other factors not peculiar to diabetes are operative to a greater or lesser extent is suggested by the observation that the average age of those with peripheral vascular complications exceeded by far that of any group with retinitis or nephropathy, the complications which may be more properly considered peculiar to diabetes, and by the observation that the duration of diabetes in those with peripheral vascular disease was shorter than in cases of nephropathy or retinopathy. Indeed, in ten cases with peripheral vascular disease diabetes was of less than five years' duration. These same ten patients were of a more advanced age (average sixty-seven years) and exhibited a lower average daily insulin dose (18 units).

Arteriosclerotic heart disease. There was definite, symptomatic arteriosclerotic heart disease in a total of seventy-three patients, or 18.5 per cent; 26.5 per cent of those forty years or older and 31.8 per cent of those fifty years or older. The sex distribution was forty-three females (19.8 per cent of all cases) and thirty males (17.0 per cent of all cases). That the incidence of arteriosclerotic heart disease in female diabetics is at least equal to the incidence in diabetic males is well known[31, 32] and is in contrast to the much higher incidence in males of the nondiabetic population.

Angina pectoris. There were thirty-six cases of angina pectoris, an incidence of 9.1 per cent, or 12.3 per cent of those forty years or older. Fifteen patients presented evidence of an old or recent myocardial infarction. The average age of all patients with angina was 61.2 years, and the average duration of diabetes was 11.6 years. In twelve cases there was accompanying hypertension.

Myocardial infarction. In thirty-four diabetic subjects there was old or recent myocardial infarction, an over-all incidence of 8.6 per cent, or 11.3 per cent of those forty years of age or over and 12.4 per cent of those over age fifty. The average age of the patients and the duration of diabetes in the group with infarction was 62.7 and 12.7 years respectively. Vascular hypertension was present in fifteen cases. The sex distribution in those with angina and/or infarction was approximately equal.

Heart failure. Findings or history indicated the present or past existence of heart failure in thirty female and thirteen male patients with arteriosclerotic heart disease. The observation that hypertension was almost twice as common in females with arteriosclerotic heart disease (twenty-three females, twelve males) and in females of the entire series (see below) suggests that this factor may have contributed appreciably to the greater frequency of heart failure in females.

Evidence of the widespread occurrence of atherosclerotic changes is shown by the presence of peripheral vascular complications in twenty-nine, or 39.7 per cent, of those with arteriosclerotic heart disease.

The effect of age and duration of diabetes upon the incidence of arteriosclerotic heart disease is illustrated in figure 5. It is evident that both age and duration of diabetes increased the incidence of arteriosclerotic heart disease and that the effect of the former was more marked. The number of patients of the same age but with diabetes of varying durations is perhaps insufficient to demonstrate conclusively the effect of duration of diabetes upon the occurrence of arteriosclerotic heart disease, but an analysis of the ninety-eight cases in the age group sixty to seventy, wherein occurred the greatest number (thirty) of cases with arteriosclerotic heart disease, is revealing. Thus, the incidence of arteriosclerotic heart disease in these ninety-eight cases was approximately 15 per cent in those with diabetes of less than five years' duration, 37.5 per cent in those with diabetes of from five to ten years' duration, and 33 per cent in those with diabetes existing ten years or longer.

In addition to the seventy-three patients with definite, symptomatic arteriosclerotic heart disease, there were eighty-five who were asymptomatic but with one or several of the following: abnormal nonspecific electrocardiogram, X-ray evidence of a calcified aorta, an enlarged or abnormal heart shadow, or a calcific valvulitis. In such persons, the presence of arteriosclerotic heart disease seemed likely. If these were combined with the unequivocal cases, the incidence of arteriosclerotic heart disease would be 40.1 per cent of all

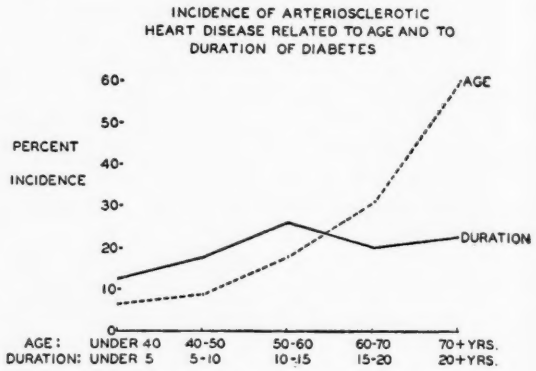

FIGURE 5

patients, 56.2 per cent of those forty years or older and 66.4 per cent of those fifty years or older.

Leibow, Hellerstein and Miller[10] have reported a 42 per cent incidence of arteriosclerotic heart disease in a group of 383 diabetic outpatients, all of whom were over forty years of age. This compares with an incidence of 26.5 per cent of our hospitalized patients who were aged forty or more. The incidence of angina and myocardial infarction in their series, however, was 10.2 and 6.8 per cent as compared with 12.3 and 11.3 per cent of the patients in our series who were in the same age group. In the present study, arteriosclerotic heart disease was considered definite only in the presence of angina pectoris, myocardial infarction or congestive heart failure associated with other evidence of extensive atherosclerosis. The figure of 42 per cent given by Liebow et al.[10] is perhaps more comparable to the one of 56.2 per cent obtained in the present investigation as representing the incidence of definite or probable arteriosclerotic heart disease in those of forty years or beyond. This figure, and the comparable incidence of 66.4 per cent for those aged fifty years or older is almost identical with the autopsy incidence reported by Bell.[5]

Vascular hypertension. A blood pressure persistently in excess of 150 mm. Hg. systolic or 90 diastolic was found in 112 subjects, or 28.4 per cent. Over age forty, the incidence was 35.6 per cent, and over age fifty it was 41.0 per cent. An increased incidence of hypertension in diabetic persons has been noted by others.[8, 9, 10, 33, 34] John, who made a study of a large number of diabetic cases over forty years of age, found a systolic pressure in excess of 150 mm. Hg. in 26 per cent of males and 50 per cent of females. Possible contributing factors noted in the present study were diabetic nephropathy, in thirty-three cases of hyperten-

sion, and arteriosclerosis, with its tendency to produce systolic hypertension. The possible role of the latter factor in producing systolic hypertension is suggested by the fact that 50 per cent of the patients with hypertension were aged sixty or over.

The sex distribution of those with hypertension was seventy-six female and thirty-six male. The possible influence of female hormones is suggested by the equal distribution below the age of fifty, but a female to male preponderance of 2.6 to 1 past this age.

DISCUSSION

The presence of definite and often multiple vascular complications in almost exactly one-half of a large number of diabetic patients, when considered without regard to age or duration of diabetes, reflects succinctly the nature of the problem of diabetes today. Improved treatment has resulted in prolongation of life to the point where vascular degenerative lesions have become increasingly evident. In this series, after twenty years or more of diabetes, over 87 per cent of the patients had definite vascular disease. Thus, whatever fundamental etiologic factors are concerned in the production of the morbid changes, it is evident that they occur, for the most part, only after a relatively long period of time. Of the factors evaluated in this series, the incidence was most affected by the duration of diabetes. A recent review and discussion of the biochemical and other factors concerned appears in the reviews by LeCompte[35] and Ricketts.[36]

The most frequently observed vascular lesion was diabetic retinopathy. The characteristic microaneurysms, if not entirely specific for diabetes,[37, 38] are certainly most common in diabetics.[13] In this investigation there was no certainty that diabetic retinopathy ever existed with diabetes of less than five years' duration, and the greatest rise in incidence took place between the tenth and fifteenth year of diabetes. Although there are no data presented in this study relative to the effects of careful control of diabetes over the years, others studying the same lesions have concluded that there is a lower incidence of retinopathy in the well controlled patients as opposed to those poorly controlled.[19b, 20, 39, 40] At present strict control appears to be the only measure which is at all effective in reducing the incidence or delaying the development of retinitis.

In common with the retinal changes, diabetic nephropathy appeared only after diabetes had been present for many years; most commonly diabetes had been present for fifteen to twenty years, and beyond twenty years there was evidence of disturbed renal function in over 28 per cent of cases. The manifestations of diabetic nephropathy are known to be variable,[16, 41] and the clinical picture is not specific. The typical nodular glomerular lesion seen in microscopic sections at autopsy or, more recently, with the aid of renal biopsy, is, however, highly specific.[6, 18, 42] LeCompte[35] has challenged the view that the renal lesion is a hyalinized saccular aneurysm similar to those seen in the retina.

In contradistinction to diabetic nephropathy and retinopathy, which are more specific for diabetes, are the atherosclerotic changes which diabetes appears to accelerate rather than cause. The incidence of arteriosclerotic heart disease correlated better with age than with duration of diabetes, although both were observed to have a positive effect upon incidence. The occurrence of vascular disease in 19.2 per cent of patients with diabetes of less than five years' duration was due to the fact that many of these patients were of an age when atherosclerotic lesions of the type found are frequently present in the absence of diabetes. Similarly, an even greater number of those with diabetes of many years' duration might have had atherosclerosis without diabetes, since they were of a more advanced age group. Bell[5] recognized this fact and indicated that only 24 per cent, and not 54 per cent, of the deaths of diabetics in his series could be attributed to the diabetic state, since 30 per cent of nondiabetics over forty years of age also die of some form of vascular disease.

The incidence of arteriosclerotic heart disease in this study was high. It is difficult to compare data on the incidence of arteriosclerotic heart disease in living subjects because criteria vary greatly.[43] It is probably better to compare the incidence of angina pectoris which was found in over 12 per cent of the patients in this investigation who were beyond age thirty-nine. The subject of myocardial infarction in diabetics has been the topic of a previous communication.[44]

The rising incidence of vascular complications demonstrated in this study and the likelihood of a continued rise as advances in treatment add years to diabetic lives indicate more than ever the need for a more fundamental understanding of the degenerative changes associated with diabetes of long standing.

SUMMARY

1. Three hundred and ninety-four hospitalized diabetic patients, selected regardless of age or duration of diabetes, were evaluated for the presence of four vascular complications: (a) diabetic retinopathy, (b) diabetic nephropathy, (c) peripheral vascular disease, and (d) arteriosclerotic heart disease.

2. At least one of these vascular lesions was found in 49.5 per cent (195 individuals). In almost one-half of these, more than one type of vascular complication existed. After twenty or more years of diabetes, 87.5 per cent of these people had one or more vascular complications.

3. Retinopathy was most frequently seen, being present in over 50 per cent of those with diabetes for ten to fifteen years and in more than 84 per cent of those with diabetes for twenty years or longer.

4. Diabetic nephropathy was present in approximately 10 per cent of all patients and in 24 per cent of those with diabetes for fifteen years or more.

5. Peripheral vascular disease was noted in 15.7 per cent of these diabetics.

6. Arteriosclerotic heart disease was present in 18.5 per cent of the series and in 26.5 per cent of those beyond age thirty-nine. Angina pectoris and myocardial infarction were present in 12.3 and 11.3 per cent respectively of patients over the age of thirty-nine. Using more liberal criteria, the likely incidence of arteriosclerotic heart disease was 56.2 per cent at age forty or more, and for those aged at least fifty, 66.4 per cent.

7. The more characteristic diabetic vascular lesions, retinopathy and nephropathy, were related chiefly to the duration of diabetes.

The vascular manifestations, arteriosclerotic heart disease and peripheral vascular disease, which are less specific for diabetes, were related in their incidence both to age of the patient and to duration of diabetes.

SUMMARIO IN INTERLINGUA

Le Complicationes Vascular de Diabete Mellite

1. Tres centos novanta-quatro hospitalisate patientes diabetic, seligite sin respecto a etate o duration del morbo, esseva evalutate in re le presentia de quatro complicationes vascular: (a) Retinopathia diabetic, (b) nephropathia diabetic, (c) morbo periphero-vascular, e (d) arteriosclerotic morbo cardiac.

2. Al minus un de iste lesiones vascular esseva trovate in 49,5 pro cento del serie (i.e. in 195 individuos). In quasi un medietate de iste casos, plus que un sol typo de complication vascular esseva presente. Post vinti annos o plus de diabete, 87,5 pro cento de iste personas habeva un o plure complicationes vascular.

3. Retinopathia esseva incontrate le plus frequentemente. Illso esseva presente in plus que 50 pro cento del individuos con diabete de un duration de inter dece e dece-cinque annos e in plus que 84 pro cento del individuos con diabete de un duration de vinti annos o plus.

4. Nephropathia diabetic esseva presente in circa 10 pro cento del serie total e in 24 pro cento del patientes con diabete de un duration de dece-cinque annos o plus.

5. Morbo periphero-vascular esseva notate in 15,7 pro cento de iste diabeticos.

6. Arteriosclerotic morbo cardiac esseva presente in 18,5 pro cento del serie total e in 26,5 pro cento del patientes con etates de plus que trenta-nove annos. Angina de pectore e infarcimento myocardial esseva presente in 12,3 e 11,3 pro cento, respectivemente, del patientes de etates de plus que trenta-nove annos. Super le base de minus exigente criterios, le incidentia probabile de arteriosclerotic morbo cardiac deveniva 56,2 pro cento inter patientes de plus que quaranta annos de etate e 66,4 pro cento inter patientes de plus que cinquanta annos.

7. Le plus characteristic lesiones vascular de diabete —retinopathia e nephropathia—esseva principalmente relationate al duration del diabete. Le manifestationes vascular que es minus specific pro diabete—i.e. arteriosclerotic morbo cardiac e morbo periphero-vascular—esseva relationate in lor incidentia al etate del patientes e al duration de lor diabete.

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Alteration of Enzyme Systems

That some enzyme systems may be altered by adaptation to changes in chemical environment has been established . . . In general, changes in enzyme systems caused by changes in type or quantity of food ingested may be expected to result in two types of adaptations, those that may be considered emergency measures, and those requiring slow changes in physiological processes. Those of the first group may consist of changes of velocity and duration of enzyme action, rate of delivery of the substrate to, and removal of the end products from, the site of action, and activation or inactivation of a reserve enzyme supply. Those of the second group may be considered adaptations in the quantities of the enzymes required to accomplish a given purpose.

From "Variations Produced by Food Differences in the Concentration of Arginase in the Livers of White Rats" by H. D. Lightbody and A. Kleinman, *J. Biol. Chem.* *129*:71-78, 1939.

Comparison of the Hyperglycemic Effects of Glucocorticoids in Human Beings

The Effect of Heredity on Responses to Glucocorticoids

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Fajans and Conn[1] recently called attention to a difference between the responses of persons with and without a family history of diabetes mellitus to glucose tolerance tests modified by prior administration of cortisone. Under the conditions of their experiment, the majority of subjects exhibited very slight impairment of glucose tolerance after cortisone. However, in a group with a positive family history of diabetes, 24 per cent of the subjects showed a substantial impairment of glucose tolerance after cortisone administration. This contrasted with a 3 per cent incidence of significant impairment in a group with no evident family history of diabetes. Hoet has reported investigations concerning the effect of cortisone on diabetes and "pre-diabetes." [2]

One of the purposes of these investigations was to evaluate the ability of a simplified glucose tolerance test as modified by prior administration of a glucocorticoid to establish the hyperglycemic potencies of glucocorticoids in human beings. Another purpose was to investigate the degree to which heredity, especially diabetic heredity, influences the response to glucocorticoids.

PROCEDURE

All subjects received a high (300 gm.) carbohydrate diet for at least three days prior to the test. Glucose was administered orally (1.75 gm. per kg. of ideal body weight). A dose of a glucocorticoid was administered by mouth eight and one-half hours and two hours before the oral glucose. The venous blood glucose was determined by the Somogyi-Nelson method[3] two hours after oral glucose. This test, then, is nothing more than a highly simplified glucose tolerance test except that a steroid is administered before the test.

The order in which the glucocorticoids were tested was not systematically randomized. However, a segment of those subjects tested consecutively to three steroids was systematically randomized (fourteen subjects, forty-two tests). Statistical analysis using the t test showed no effect of order of testing on the results. The specific dosages used in testing each of the steroids are indicated in the accompanying figures. It should be noted that the dose of the steroid was increased 25 per cent for each subject who weighed more than 160 lb. The "priming" dose of a steroid administered eight and one-half hours before the oral glucose was given in order that our data might be compared with those of Fajans and Conn. All subjects were healthy and ambulant.

RESULTS

Comparison of hyperglycemic potencies of glucocorticoids. Figure 1 shows the degree to which cortisone acetate, prednisone, and prednisolone modified glucose tolerance when given orally in a dosage ratio of 5:1:1 (50 mg. cortisone acetate, 10 mg. prednisone, and 10 mg. prednisolone). This group of thirty-nine healthy, nondiabetic subjects ranged in age from eighteen to forty-seven. Each subject had a glucose tolerance test, a cortisone-glucose test, a prednisone-glucose test and a prednisolone-glucose test.

The fairly wide variations in the responses to each of the steroids among individuals is evident. However, the responses of a particular individual to each of these three steroids were usually, although not invariably, of relatively similar magnitude. For example, a subject who exhibited a response to cortisone above the average for the group usually showed responses to prednisone and prednisolone which were also above average. Table 1 shows the data from which figure 1 was derived and is included to illustrate the variations in response to the drugs demonstrated by each test subject. It may be noted that the presence or absence of a family history of diabetes is indicated in this table.

The average responses of this group were 109 mg. per

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* From Department of Medicine, University of Oklahoma School of Medicine and Veterans Administration Hospital, Oklahoma City, Oklahoma.

TABLE 1

Results of glucocorticoid-modified glucose tolerance tests

Subject No.	Age	Family history of diabetes	Sex	Two-hour blood glucose in mg. per cent: Control tests after oral glucose	Cortisone-glucose test	Prednisone-glucose test	Prednisolone-glucose test
1	24	No	M	71	104	146	136
2	24	No	M	84	114	132	128
3	21	No	F	74	146	120	116
4	24	No	M	71	96	180	114
5	30	No	M	74	108	124	104
6	25	No	M	76	80	100	96
7	24	No	M	80	142	88	96
8	23	No	M	84	80	76	84
9	23	No	M	92	88	132	108
10	27	No	M	100	80	156	84
11	26	No	M	52	100	124	124
12	28	No	M	80	80	100	76
13	23	No	M	92	114	120	124
14	25	No	M	88	92	116	116
15	21	No	M	100	104	72	116
16	43	No	M	100	146	180	142
17	28	No	M	71	48	114	84
18	37	No	M	76	92	120	108
19	38	No	M	52	96	76	74
20	33	No	M	76	114	172	84
21	31	No	M	71	192	88	132
22	35	No	F	60	146	114	200
23	24	Yes	M	65	75	100	120
24	23	Yes	M	79	142	124	96
25	23	Yes	M	60	66	74	84
26	18	Yes	F	108	172	208	192
27	32	Yes	F	80	114	200	280
28	36	Yes	F	76	160	204	187
29	40	Yes	F	80	132	100	120
30	28	Yes	F	74	108	104	176
31	30	Yes	F	71	76	132	108
32	24	Yes	F	71	114	187	142
33	39	Yes	M	104	88	166	128
34	40	Yes	F	92	88	100	116
35	18	Yes	F	104	108	180	172
36	28	Yes	M	84	124	136	120
37	21	Yes	M	76	84	76	120
38	21	Yes	F	54	114	88	56
39	47	Yes	F	100	124	120	172

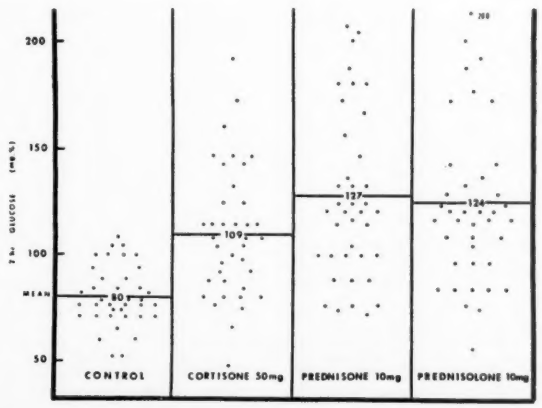

FIG. 1. The effect of glucocorticoids on glucose tolerance. Each dot represents a blood glucose value obtained two hours after ingestion of glucose. Each of thirty-nine subjects was tested on four occasions. In the first column marked "control" their responses to oral glucose alone are represented. In the remaining columns are presented the response of these same subjects to subsequent tests modified by prior administration of a glucocorticoid.

cent after cortisone, 127 mg. per cent after prednisone, and 124 mg. per cent after prednisolone. Statistical analysis indicates that the difference between the responses to prednisone and prednisolone was not significant ($p = 0.6$-0.7). The responses to both prednisone and prednisolone were significantly greater than the responses to cortisone (p value for prednisone $= 0.02$-0.01; p value for prednisolone $= 0.02$-0.025).

A clearer representation of the responses of this group to these steroids is obtained by expressing the responses as milligrams per cent above the control level. After cortisone plus oral glucose these subjects showed two-hour glucose values which were, on the average, 29 mg. per cent above the values after glucose alone. Prednisone and prednisolone caused elevations above the control levels which averaged 47 mg. per cent and 44 mg. per cent respectively. It may be noted that prednisone and prednisolone modified glucose tolerance to the same degree while both were decidedly more potent than cortisone even though the dose of cortisone acetate was five times greater. (Since 50 mg. of cortisone acetate contains approximately 44 mg. of cortisone, the steroids were actually compared in a ratio of 4.4 of cortisone to one to one.)

Figure 2 shows the blood glucose responses of fourteen subjects, each of whom had two glucose tolerance tests (blood glucose two hours after oral glucose), one after 40 mg. of hydrocortisone and another after 10 mg. of prednisone. The average two-hour glucose value after prednisone was 137 mg. per cent as compared to 145 mg. per cent after hydrocortisone. This difference is not of statistical significance, having a p value of greater than 0.7. These data suggest that the hyperglycemic potency of prednisone (and by inference prednisolone) is four times that of hydrocortisone. It may be noted that the mean response to prednisone of the subjects in figure 2 (137 mg. per cent) was greater than the mean response of those in figure 1 (127 mg. per cent). This was probably due to the fact that the results shown in figure 2 were from tests done on a group in which the majority of the subjects had a strong family history of diabetes (see figure 4). A control test (blood glucose two hours after glucose load without prior administration of a drug) was not done in each of these fourteen subjects. However, it was done in eleven instances and the mean value was 85 mg. per cent.

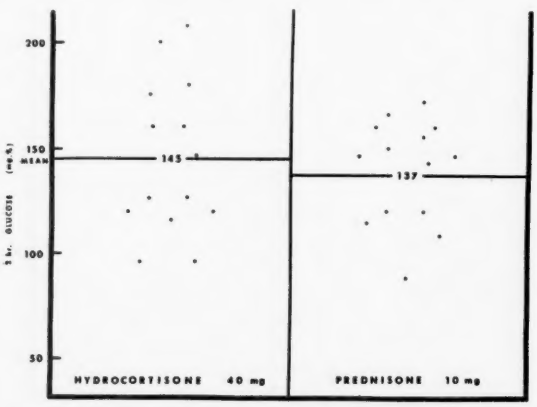

FIG. 2. Comparative responses (two-hour blood glucose) of fourteen healthy subjects each of whom had a hydrocortisone-modified and a prednisone-modified glucose tolerance test. See procedure for technic of testing.

A group of seven subjects were given a glucose tolerance test after 2 mg. of 9-alpha-fluorohydrocortisone. None of the seven showed any hyperglycemic responses to this dose of the drug. This indicated that 9-alpha-fluorohydrocortisone was very definitely less than twenty times as hyperglycemic as hydrocortisone in humans.

The ability of this method to distinguish relatively small differences in hyperglycemic potencies was tested further by comparing the responses of healthy adults to 40 mg. hydrocortisone and 50 mg. of cortisone acetate. Since the response of each subject was greater than hydrocortisone the data were analyzed after six subjects had been tested with both drugs. The p value was less than 0.01 indicating a difference in potencies had been identified after only twelve blood glucose determinations.

An effect of age on steroid-modified glucose tolerance has not been previously reported. Our preliminary studies have indicated that older subjects are more likely to exhibit a "positive" response. Sufficient data are not available at present to describe clearly the effect of age on the response to such tests, since we have tested very few subjects over fifty or under twenty. In order to test the effect of age on the response to cortisone-glucose tolerance tests, all of the nondiabetic healthy subjects who had had this test were divided into two groups. The younger (below age thirty-one) showed two-hour glucose levels which averaged 17 mg. per cent above the control levels. The older subjects (above age thirty) had levels averaging 59 mg. per cent above control levels. Analysis of results in other groups concerning the effect of age on various types of steroid-glucose tolerance tests showed less significant differences but a positive correlation of some degree was consistently seen.

The influence of heredity on responses to glucocorticoids. The lack of influence of a family history of diabetes on responses of a small group of subjects to cortisone-glucose tolerance tests is illustrated in figure 3. The groups were carefully matched for age. The mean

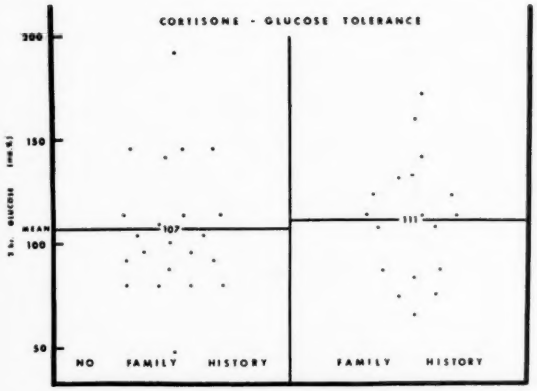

FIG. 3. A comparison of responses of twenty-two subjects having no family history of diabetes with those of seventeen individuals having diabetes in their families to a cortisone-glucose tolerance test. All subjects were nondiabetic.

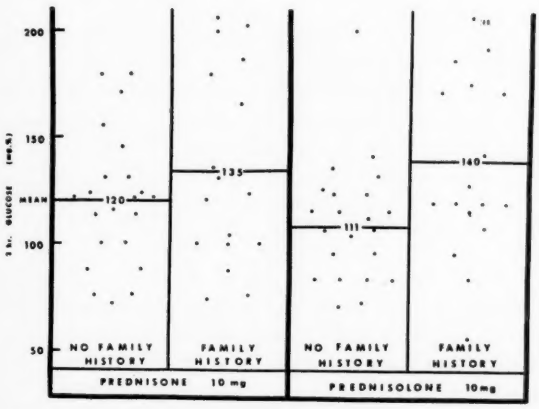

FIG. 4. A further comparison of the response of subjects represented in figure 5 to glucose tolerance tests as modified by prednisone and prednisolone.

age for the group with a diabetic parent, sibling or child was twenty-nine (range 18 to 47), while the mean age of the subjects with no family history of diabetes was twenty-eight (range 21 to 43). The mean values were 107 mg. per cent for a group with no family history of diabetes and 111 mg. per cent for those with a family history of diabetes. Although cortisone-modified glucose tolerance test results were very slightly higher in the group with a diabetic parent, sibling or child, the difference between the groups is not statistically significant.

Our results resemble closely those reported by Fajans and Conn in that 20 per cent of the group with a family history had a two-hour glucose above 140 mg. per cent as compared to 24 per cent of their subjects with a similar family history. However, responses above 140 mg. per cent in their group with no family history of diabetes were rare (3 per cent), whereas our subjects with a negative family history exhibited values above 140 frequently (23 per cent). The results of investigations done by us more recently than those reported here suggest that the incidence of a "positive" response to cortisone in persons with no family history of diabetes may not be as great as was suggested by the results in this small group. Furthermore, the data of Fajans and Conn include a larger, and thus a statistically more reliable, sample.

Figure 4 shows that a group with a diabetic parent, sibling or child exhibited greater responses to both prednisone and prednisolone than did a group with a negative family history. The mean responses of the subjects with and without a positive family history were 135 mg. per cent and 120 mg. per cent after prednisone, while the mean values after prednisolone were 140 mg. per cent and 111 mg. per cent respectively. Statistical analysis showed that the group with a family history of diabetes exhibited a significantly greater response to both prednisone ($p < 0.02$) and prednisolone ($p < 0.01$) when compared to the control group.

It seemed important to study further the degree to which the response to glucocorticoids was conditioned by heredity, especially by diabetic heredity. For this reason preliminary studies are under way utilizing several special groups of subjects including (a) identical twins and (b) persons with a diabetic mother and father.

The responses of identical twins to steroid-glucose tolerance testing are strikingly similar. Results of testing carried out in ten pairs of identical twins (twenty subjects) were analyzed statistically with the following findings: (1) The responses of the pairs to the control test (to oral glucose alone) were significantly correlated ($r = 0.67$). (2) The responses of the pairs to prednisone were significantly correlated ($r = 0.58$; $p = 0.05$). This latter positive correlation is of great interest since effect on blood glucose produced by the glucose load per se was separated from the effect of prednisone. This was done by defining the response to prednisone as "glucose excess" produced by prednisone plus oral glucose above that produced by glucose loading alone. This suggests that heredity conditioned the response to the steroid itself.

The statistically significant correlations established for these twin pairs was not due to the equality in age of each twin and his twin. The method used in calculating this correlation took into account the effect of age in the total group before yielding the final correlation results.

The degree of similarity between the responses of twin

and twin was tested further in the following manner. First of all, the response of each twin to the corticoid was identified by determining the degree to which the drug elevated the blood glucose above the control value. The differences between the responses of twin and twin was compared and in the first pair found to be 4 mg. per cent, 4 mg. per cent and 10 mg. per cent for cortisone, prednisone and prednisolone respectively, whereas the differences between the responses of one of these twins (randomly selected) and ten randomly selected young adults were far greater. These averaged 27 mg. per cent, 50 mg. per cent, and 28 mg. per cent for cortisone, prednisone and prednisolone respectively.

The similarity between the second pair of twins tested was also analyzed in this manner. The differences between twin and twin were 10 mg. per cent, 16 mg. per cent and 2 mg. per cent. The difference between one of this pair and ten randomly selected young adults averaged 43 mg. per cent, 49 mg. per cent and 28 mg. per cent.

Studies on twins will not yield, of course, specific information concerning diabetic heredity until a sufficient number of identical twins with diabetic heredity are tested.

The ability of the steroid-glucose tolerance test to identify potential diabetics is being tested further by studying a group of subjects (four families) by glucose tolerance testing as modified by prednisone are shown in figure 5. It may be noted that although both of these groups exhibited greater responses to the test than did subjects with no family history of diabetes, the group whose mother and father were both diabetic showed no tendency toward greater responses than those subjects with a much less significant family history of diabetes mellitus. The responses of these two groups to cortisone-glucose tests were also comparable. If a larger number of subjects with two diabetic parents show no greater propensity to respond "positively" to steroid-glucose tolerance testing than has been exhibited by this small group then it is likely that such testing will have a limited specificity for identifying potential diabetes.

A nondiabetic subject who had exhibited a marked response to other glucocorticoids was given a glucose tolerance test after prior administration of 2 mg. of 9-alpha-fluorohydrocortisone. Even though seven previous subjects had shown no response, this subject had a two-hour blood glucose 44 mg. per cent higher after the fluorohydrocortisone-glucose test than after the glucose alone. This subject's mother (also nondiabetic) responded significantly to the same dose of fluorohydrocortisone. The latter two test results are described in order to cite examples of nondiabetic subjects who display unusual

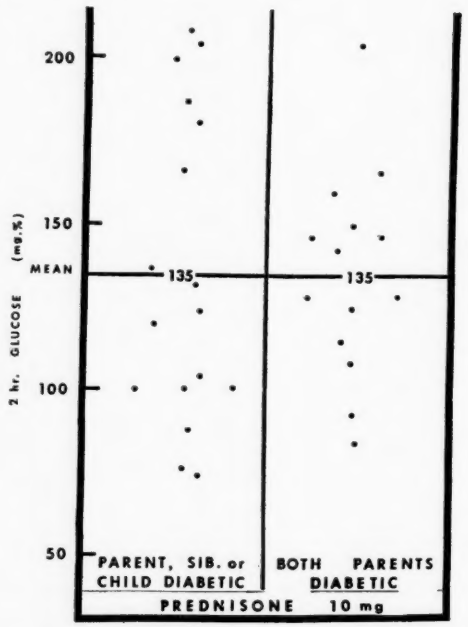

FIG. 5. A comparison of the results of prednisone-glucose tolerance testing in two groups with different degrees of diabetic heredity. Results in the first column are in subjects giving a history of diabetes in a child, sibling or single parent. In the second column, the results in subjects having two diabetic parents are presented.

sensitivity to small amounts of glucocorticoids. They also suggest that this tendency is to some degree conditioned by heredity (in this instance possibly diabetic heredity since there was a strong family history of diabetes).

DISCUSSION

The 50 mg. dose of cortisone acetate had been selected in order that these results might be compared with those of Fajans and Conn. The doses of the other glucocorticoids were chosen because their "organic metabolic-regulating potencies" were roughly similar to the potency of 50 mg. cortisone acetate and because tablets were readily available for oral administration at these dosages.

The ability of this method to identify small differences between the hyperglycemic potencies of 10 mg. prednisone and 50 mg. cortisone acetate on the one hand and between 40 mg. hydrocortisone and 50 mg. cortisone acetate on the other is impressive, especially since this difference was established by testing only a few subjects. A fairly large number of tests is necessary to establish accurately the hyperglycemic potency of a glucocorticoid if the potency is to be estimated by measuring the responses of a group of subjects to various doses of the

steroid. However, if the same subjects are tested with both a known and an unknown steroid, an accurate estimation of the hyperglycemic potency may be obtained after as few as twenty tests. When subjects are available whose sensitivities to a glucocorticoid of known potency (such as hydrocortisone) have already been established, it should be possible to estimate fairly accurately the potency of an unknown after administering it to a very few subjects. It was, for example, possible in one day to show that 9-alpha-fluorohydrocortisone was definitely less than twenty times as potent as hydrocortisone by testing seven subjects.

New glucocorticoids to be tested subsequently could conceivably exhibit a lack of correlation between their hyperglycemic potencies on the one hand and their anti-inflammatory and pituitary inhibiting potencies on the other. However, it may be noted that the hyperglycemic potencies of these glucocorticoids closely approximate their other "organic metabolic-regulating" potencies which were established previously by more elaborate methods. For example, these results suggest that prednisone and prednisolone are of equal hyperglycemic potency, and that both of these drugs are four times more potent than hydrocortisone. It is of interest that this same ratio has previously been established for the anti-inflammatory potencies of these three glucocorticoids. This type of procedure, then, may be a convenient way of estimating the "organic metabolic-regulating potency" of a glucocorticoid.

SUMMARY AND CONCLUSIONS

The carbohydrate metabolism regulating (or hyperglycemic) potency of a steroid may be quickly and easily estimated by testing the degree to which it modifies glucose tolerance (as measured by a single blood glucose determination two hours after glucose by mouth). The hyperglycemic potency of a steroid may be accurately estimated by testing only a few subjects if they are tested to both a known and an unknown steroid with similar characteristics of time-action.

Using such a method the carbohydrate metabolism regulating potencies of oral prednisone and prednisolone were measured and no significant difference found.

Under the circumstances of this experiment prednisone and prednisolone were more than five times more potent than cortisone acetate in their hyperglycemic effects. Prednisone and hydrocortisone were identical in effect when administered orally in a dosage ratio of one to four.

Older subjects showed a "positive" response to this steroid-glucose test more frequently than younger.

The strikingly similar responses of identical twins to glucose tolerance tests and to steroid-glucose tolerance tests suggest that heredity plays a significant role in conditioning the hyperglycemic response both to glucose loading and to glucocorticoids.

Nondiabetic subjects with a family history of diabetes showed significantly greater hyperglycemic responses to prednisone and prednisolone-glucose tolerance tests than a control group.

The responses to prednisone-glucose tolerance testing of fourteen subjects with a positive family history were no greater than the responses of subjects with a much less significant family history. These latter data are not adequate to permit a final conclusion but suggest that the steroid-glucose tolerance test has a limited ability to predict the eventual development of diabetes.

Although long-term follow-up of persons who exhibit both "positive" and "negative" responses to tests is planned, it is hoped that the degree to which the responses to steroids are conditioned by diabetic heredity may be elucidated at an earlier date by using the methods resembling those described above.

SUMMARIO IN INTERLINGUA

Comparation del Effectos Hyperglycemic de Glucocorticoides in Humanos: Le Effecto del Hereditate Super le Responsa a Glucocorticoides

Le potentia del effecto regulatori que es exercite per un steroide super le metabolismo de hydratos de carbon —i.e. su potentia hyperglycemic—pote esser estimate facile- e rapidemente per testar le grado a que illo modifica le toleration de glucosa (mesurate per medio de un sol determination de glucosa sanguinee duo horas post le administration de glucosa per via oral). Le potentia hyperglycemic de un steroide pote esser estimate accuratemente per testar solmente un parve numero de subjectos, providite que le tests es executate con duo steroides—le un cognoscite, le altere non—que possede simile characteristicas quanto al conditiones temporal de lor action.

Per medio de un tal methodo le potentia de regular le metabolismo de hydratos de carbon esseva mesurate pro prednisona e prednisolona in administrationes oral. Nulle differentia significative esseva trovate.

Sub le conditiones de iste experimento, prednisona e prednisolona se monstrava plus que cinque vices plus efficace que acetato de cortisona in lor effectos hyperglycemic. Prednisona e hydrocortisona esseva identic in lor effectos quando illos esseva administrate oralmente in doses del proportion de un a quatro.

Personas de etates plus avantiate monstrava responsas "positive" in iste test de steroide e glucosa plus fre-

quentemente que plus juvene subjectos.

Le frappantemente simile responsas de geminos identic a tests de toleration glucosic e a tests de toleration steroido-glucosic suggere que le hereditate es un factor de importantia in conditionar le responsa hyperglycemic a cargas de glucosa e etiam a glucocorticoides.

Subjectos nondiabetic con historias familial de diabete monstrava significativamente plus marcate responsas hyperglycemic a prednisona e prednisolona in iste tests que un gruppo de controlo.

Le responsas in tests de toleration a prednisona-glucosa in dece-quatro individuos con positive historias familial non esseva plus pronunciate que le responsas de subjectos con multo minus significative historias familial. Iste datos non suffice pro justificar le derivation de conclusiones final, sed illos suggere que le test de toleration steroido-glucosic es limitate in su poter de predicer le disveloppamento futur de diabete.

Ben que observationes consecutori a longe duration es planate con gruppos de personas que exhibi responsas positive o qui exhibi responsas negative, il es a sperar que le grado a que le responsas a steroides es conditionate per un hereditate diabetic pote esser elucidate plus rapidemente per medio de methodos simile a illos describite in le presente reporto.

ACKNOWLEDGMENT

The author would like to acknowledge the technical assistance of William Hood, Sandra Chiles and Richard Cahill.

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DISCUSSION

STEFAN S. FAJANS, M.D., (*Ann Arbor, Michigan*): I have been most interested in Dr. West's study on the effect of carbohydrate-active adrenal steroids on glucose tolerance in human subjects. Dr. West permitted me to see his slides yesterday evening. In general, Dr. West has found differences in response to adrenal steroids between the two groups of subjects, namely, those without a family history of diabetes as compared with those nondiabetic subjects with a family history of diabetes.

This would be in line with the findings that we reported before this society three years ago. As we mentioned at that time, the question of various time dose schedules had to be explored further; I am very happy to see Dr. West has done this. In order not to introduce further variables, we have not changed our technic so far. Now, Dr. West's study does bring out those differences in steroid dosages as far as response is concerned.

In our group of 100 controlled subjects without a family history of diabetes, we found three individuals who gave a positive response following cortisone. I mean in a two-hour blood sugar more than 140 mg. per cent.

Dr. West found a much higher incidence of positive responses in subjects without a family history of diabetes, if I remember correctly about five out of twenty-five.

The following differences between our studies have occurred to me. First of all, Dr. West's study indicated patients above age thirty gave a higher incidence of response than younger ones. In our series only one individual among a good number of controlled subjects above the age of thirty gave a positive response. Also in our subjects with a family history of diabetes there didn't seem to be much change in incidence of response by age; so there seems to be some disagreement in findings.

Another difference is that Dr. West's subjects received three courses of steroids on alternate days: cortisone, prednisone and prednisolone in various sequences.

Now, he has told me that as a group these responses to cortisone were the same irrespective of the order of administration of these steroids. This seems to be an important difference in our approaches when it comes to evaluating individual subjects rather than a group. Giving steroids daily and repeating the glucose tolerance test, we certainly get modifications in our responses.

Dr. West also mentioned the close parallelism between the increase in blood sugar following cortisone and prednisone and prednisolone irrespective of family history. If there was such a close parallelism, why did he get differences in response with prednisone and prednisolone, but not with cortisone?

One also wonders whether the patients with negative family history have the same incidence of familiarity with background in Oklahoma as in Michigan. This is something you certainly can't settle.

When one does only a two-hour blood sugar determination in a control test, one may include individuals who might under complete glucose tolerance test give a high peak, but have a normal two-hour blood sugar. Such individuals would not be called diabetic by us, but would certainly be eliminated from a control group.

Since he was dealing with four families, I don't believe the data on bilateral incidence of family history of diabetes quite justify any conclusion. In our series of

individuals with a family history of diabetes, we discovered previously undiagnosed diabetes in 20 per cent.

Dr. West did not mention anything about the incidence of previously undiagnosed diabetics which, of course, would have to be eliminated for testing.

DR. WEST: I should like to say I don't think this study in any way detracts from the value of the finding of Dr. Fajans, that a family history of diabetes affects the incidence of "positive" response to glucocorticoids. I think if we tested more persons to cortisone modified tests, that our results would be more nearly similar to those of Dr. Fajans. A somewhat greater percentage of our people tested to the cortisone modified test were over thirty, and that would explain a minor part of the so-called discrepancy between his figures and ours.

In regard to the order of testing, our routine was always to skip a day between the tests, and we felt with these small doses and with skipping a day, there would be little likelihood of any cumulative effect of diet or steroids in either a positive or a negative manner.

We tested this by systematically randomizing forty-two tests, and then we analyzed the control figure, the cortisone figure, the prednisone figure and prednisolone figure and found that the results were the same in each instance. So I believe, if there is a discrepancy, it is not because of the order of testing.

In regard to the appearance of previously undiscovered diabetes in each of the groups, our results were rather similar to those reported by Dr. Fajans. I am sorry I don't have the exact figures. My guess would be that in screening our subjects with a diabetic parent, sibling or child, we found about 15 per cent of these supposedly healthy people to have glucose tolerance impairment, and they were discarded from the study.

In screening the group with two diabetic parents, we found that approximately 20 to 25 per cent had diabetes, and, of course, they were not included in this study since we were testing for potential diabetes.

Diabetes and Insulin

The possible alteration of enzymes in animals with diabetes mellitus has long been considered. Foster in 1867 found no change in the blood amylase in six cases of diabetes. In commenting on his findings, he remarked that "the disease diabetes is due not to any excess but rather to some modified action of ferment." It is interesting that at such an early date Foster was already considering disease in terms of enzyme alterations. In subsequent years, and especially before the discovery of insulin, many other studies reported increases, decreases, or no change in the blood amylase level. Some of these works were cited by Roe, Smith and Treadwell. These studies confirmed Foster's original observation, in that there was no change in blood amylase in depancreatized or alloxan diabetic rats. The amylase activity in pancreas and salivary gland has also been studied in relation to insulin action. The so-called amylase activities of several other tissues are probably not referable to diastatic action.

Changes in concentrations have been found of enzymes whose function is related to carbohydrate metabolism. Such a change is that of glucose-6-phosphatase. Ashmore, Hastings, and Nesbett (Ashmore, J., Hastings, A. B., and Nesbett, F. B.: The effect of diabetes and fasting on liver glucose-6-phosphatase. Proc. Nat. Acad. Sc. *40*:673-78, 1954) have come to the conclusion that:

". . . the increased concentration of glucose-6-phosphatase in diabetic liver could be returned toward normal by the in vivo injection of insulin. In vitro insulin was without effect. This suggests that liver glucose-6-phosphatase was elevated in the diabetic liver due to general metabolic changes that occur in diabetes.

"The nature of the changes in glucose-6-phosphatase that occur in diabetes suggests that this enzyme adapts in response to a decreased ability of the peripheral tissues to utilize glucose, thus bringing about an increase in the concentration of blood sugar. In fasting, glucose-6-phosphatase acts to release glucose arising from both glycogenolytic and gluconeogenic processes. In diabetes the increase in this enzyme offers evidence for the overproduction of glucose believed to occur in this disease."

From "Enzymatic and Metabolic Adaptations in Animals" by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* *36*:164-254, 1956.

The Preservation of Blood Sugar for Diabetes Detection

Nathan Kantor, Ph.D., and Hugh L. C. Wilkerson, M.D.,† Boston*

A satisfactory preservative for blood sugar is needed for blood specimens that are not analyzed before significant glycolysis occurs. Since the concentration of blood sugar is of primary importance in the diagnosis of diabetes, its chemical determination must be accurate and not subject to undue influences. In a diabetes detection program as well as in clinical medicine it may be desirable to collect blood specimens and transport them to a central laboratory for analysis. Since the amount of glycolysis is related to time and since a varying period of time would elapse between the collection of the blood and its analysis, the need for a substance that would inhibit glycolysis for an appreciable length of time is evident.

A review of literature revealed considerable disagreement concerning the merits of various preservatives.[1–13] However, many investigators have agreed on the usefulness of fluoride. Most of them used sodium fluoride under varying conditions [2, 3, 5, 6, 7, 10–13] with a few using the more soluble potassium fluoride. [8, 9] Some of the discrepancies are probably due to the small number of specimens used by the investigators and to the inaccuracies in the methods of analysis. In this paper, an investigation is reported comparing the efficacy of four preservatives, viz., sodium fluoride and potassium fluoride, with and without thymol, to inhibit glycolysis in whole blood.

PROCEDURE

Approximately thirty milliliters of blood were drawn from patients of the Diabetes Clinic of the Boston City Hospital selected at random. Seven milliliters of blood were added to each container which had previously been prepared as follows: 70 mg. of NaF were weighed on an analytical balance and put into one batch of individual test tubes; 112 mg. of $KF.2H_2O$ were similarly added to another batch of individual tubes. To half of these tubes was added 0.01 ml. of an alcoholic solution of thymol (70 per cent w/v). The concentration of the preservatives was thus:

10 mg. KF per ml. of blood
10 mg. KF and 1 mg. thymol per ml. of blood
10 mg. NaF per ml. of blood
10 mg. NaF and 1 mg. thymol per ml. of blood.

The initial blood sugar determinations were started within an hour after the collection of bloods using the Somogyi-Nelson procedure.[14] The tubes were then mailed from the laboratory, so that they went to the post office and were returned the following morning. Two series of bloods were taken. In the first phase, fifty-one specimens were collected on ten Mondays and blood sugar determinations were repeated 24, 48, 72 and 96 hours afterwards. In the second phase, fifty-six specimens were collected on eight Fridays and blood sugar determinations were repeated after 72, 96, 120 and 144 hours had elapsed. The blood specimens were kept at room temperature between determinations.

RESULTS

The mean of the original four blood sugar determinations was used as an estimate of the "true" blood sugar level, as a base line to determine the efficacy of the four preservatives. An additional experiment showing the immediate effects of sodium fluoride and potassium fluoride as compared to an immediate determination with no preservative showed a mean difference of —.20 per cent for sodium fluoride and —1.65 per cent for potassium fluoride. This small effect indicated that to use the mean of the four original determinations would introduce an error of only 0.7 per cent.

To determine the efficiency of the preservative in preventing glycolysis, the distributions at the various time intervals for the four preservatives were compared to the distribution of the one-hour readings by use of the Chi Square (x^2) test. Thus we were able to test whether the difference between the various distributions could have been due to laboratory procedures. The results of

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these tests showed that all the distributions were significantly different from the one-hour distribution at the .01 probability level. This means that it is highly probable that the preservatives do not completely prevent glycolysis, for the means of all the distributions were lower than the means of the one-hour distribution.

Although the preservatives probably did not prevent glycolysis, they did inhibit this action and therefore can be quite useful. The per cent of blood sugar values that did not differ from the "true" blood sugar value by a given per cent (4, 6, 8 and 10 per cent) after specific time intervals (24 through 144 hours) are shown on table 1 for the bloods drawn on Mondays and table 2 for the bloods drawn on Fridays. From the last column in both tables it will be seen that almost all the blood sugar levels will be maintained within the 10 per cent limit up to 144 hours. Within the 8 per cent limit, 86 per cent or more of all the specimens were maintained under the conditions of the experiment.

It can be noted from the tables that the preservative action on Fridays' bloods after comparable times was better than that on Mondays' specimens. This raises the question as to what effect the multiple withdrawal of blood from a test tube had on the glucose level in this particular experiment.

Bacterial contamination may have been introduced, since nonsterile pipettes were used to measure the blood. If this is so then the single pipetting of blood after a period of four to six days, as would probably be done in field conditions, should yield results somewhat better than those presented here.

DISCUSSION

Although none of the four substances completely prevents the degradation of the blood sugar, any one of them may be used to inhibit glycolysis in blood for several days so that the blood sugar level would not be much different from the original value.

The temperature has considerable bearing on the preservative action of any of these substances. Low temperature retards the rate of glycolysis and thus enhances the preservative action. Since the study, which involved mailing the specimens, was not under temperature control, some of the inconsistent results may be due to exposure to varying temperatures encountered in the transportation. The degree of contamination by microorganisms directly affects glycolysis. Roe, et al., reported that preservation is favorably influenced by sterile conditions.[10] In some of our previous work we have found this to be true.

However, the use of sterile technic in holding blood samples is often impractical from the technical aspect.

The concentration of 10 mg. of the fluoride salt per ml. of blood is a convenient one because of its satisfactory anticoagulant effect. Preliminary work in our laboratory with concentrations below 10 mg. per ml. of blood yielded unsatsifactory results.

The effect of sodium fluoride was similar to that of potassium fluoride. It was noted, however, that the initial blood sugar concentrations of the bloods containing the potassium salt were somewhat lower than those of the bloods with the sodium salt. This slight discrepancy is due, we believe, to the fact that the two salts were weighed on an analytical balance. Since potassium fluoride is used as a hydrate ($KF.2H_2O$) and is also hygroscopic, a small experimental error due to dilution is introduced, but this error is insignificant. There is also a very slight error of dilution introduced by the addition of 0.01 ml. of alcoholic thymol. A check was made to determine the effect of the two fluoride salts upon the Somogyi-Nelson method but no such effect was found.

The individual weighing is laborious and time-consuming. It is more convenient to add aliquots of almost saturated solutions to the blood bottle and evaporate the solution. Sodium fluoride can be prepared as a 4 per cent solution whereas potassium fluoride can be prepared as an 80 per cent solution (80 per cent $KF.2H_2O$ corresponds to 50 per cent KF.) Thus 1.25 ml. of the sodium fluoride solution is required for 5 ml. of blood whereas only 0.1 ml. of the potassium fluoride solution is necessary. Since the potassium fluoride solution is quite alkaline, it should be evaporated at low temperature (50° C.) overnight, otherwise it will react with the glass. It is advisable to store the concentrated solution in a polyethylene container for the same reason. If facilities for evaporation are not available, it may be found convenient to add 0.1 ml. or two drops of a saturated potassium fluoride solution to the blood bottle and make a correction of 2 per cent.

Ordinarily potassium fluoride is the preservative of choice when complete evaporation is feasible. Since sodium fluoride does not absorb moisture from the air, it is preferable where dry powder is to be used in preparing the tubes. Because sodium fluoride is somewhat insoluble, it is important to shake the sample thoroughly in order to prevent clotting.*

*Thymol has been reported to interfere, under certain conditions, with the Wilkerson-Heftmann screening method. For this reason either sodium or potassium fluoride alone is recommended when this test is used. Fortunately, thymol does not enhance the preservative effect of either fluoride compound.

TABLE 1

Distribution of percentage of blood sugar readings falling within specified limits by preservative and time after bloodletting—for fifty-one blood specimens drawn on Mondays

Preservative	Hours after bloodletting	Percentage of reading within indicated limits of original blood sugar level ± 4 per cent	± 6 per cent	± 8 per cent	± 10 per cent
Potassium fluoride	24	58	78	91	97
	48	57	79	92	98
	72	62	86	97	99
	96	60	80	92	98
Potassium fluoride and thymol	24	79	95	99	100
	48	72	90	97	99
	72	66	85	94	99
	96	56	77	89	96
Sodium fluoride	24	71	89	97	99
	48	61	81	92	97
	72	77	93	99	100
	96	64	83	93	98
Sodium fluoride and thymol	24	70	88	96	99
	48	54	73	86	93
	72	61	81	92	97
	96	54	74	86	94

TABLE 2

Distribution of percentage of blood sugar readings falling within specified limits by preservative and time after bloodletting—for fifty-six blood specimens drawn on Fridays

Preservative	Hours after bloodletting	Percentage of reading within indicated limits of original blood sugar level ± 4 per cent	± 6 per cent	± 8 per cent	± 10 per cent
Potassium fluoride	72	68	87	96	99
	96	75	92	98	100
	120	63	83	93	98
	144	57	79	92	98
Potassium fluoride with thymol	72	73	90	97	99
	96	75	92	98	100
	120	76	92	98	100
	144	75	93	99	100
Sodium fluoride	72	71	89	97	99
	96	72	90	97	99
	120	68	87	95	99
	144	68	87	96	99
Sodium fluoride with thymol	72	77	93	98	100
	96	74	91	98	100
	120	65	84	94	98
	144	65	84	94	98

SUMMARY

1. A comparison was made of the efficacy of four preservatives, potassium fluoride, potassium fluoride with thymol, sodium fluoride and sodium fluoride with thymol in inhibiting glycolysis in transported blood specimens.

2. All four substances had approximately the same efficacy.

3. Blood sugar levels were maintained within 10 per cent of the original value in almost all the blood specimens for periods up to 144 hours. Eighty-six per cent or better of the blood sugar values were maintained within 8 per cent.

4. Although these substances do not completely prevent glycolysis, they are sufficiently inhibitory to make them clinically useful in blood sugar analysis and diabetes detection.

SUMMARIO IN INTERLINGUA

Preservation de Sucro Sanguinee pro le Detection de Diabete

1. Esseva comparate le efficacia de quatro agentes in le inhibition de glycolyse in specimens de sanguine. Le agentes esseva fluoruro de kalium, fluoruro de kalium con thymol, fluoruro de natrium, e fluoruro de natrium con thymol.

2. Le quatro substantias habeva approximativemente le mesme grado de efficacia.

3. Le nivellos de sucro sanguinee in quasi omne le specimens esseva mantenite durante usque a 144 horas intra un margine de 10 pro cento. Octanta-sex pro cento del valores (o plus) esseva mantenite intra un margine de 8 pro cento.

4. Ben que iste substantias non preveni glycolyse completemente, illos es sufficientemente inhibitori pro esser de valor clinic in le analyse de sucro sanguinee e le detection de diabete.

ACKNOWLEDGMENT

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The Bony Skeleton and Body Weight

A final contributor to confusion about the meaning of the total body weight is the bony skeleton. The mineral mass in the skeleton averages something like 6 per cent of the normal body weight of the adult but it may be as low as 4 per cent or as high as 9 per cent.[1] There is no evidence that these variations are in any way related to relative obesity except insofar as they may be erroneously included in the inference of obesity from gross body weight.

Perhaps a more important contribution of the skeleton to the body weight is through its form. Relative body weight and overweight and underweight are commonly computed on the basis of weight for height. But a broad and short skeleton automatically means a large body weight per unit of height and no system has yet been devised to allow for this in a practical manner.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "Body Weight, Body Composition and Calorie Status" by Ancel Keys, Ph.D., p. 15.

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SPECIAL ARTICLES

Vascular Disease
Panel Discussion

Arthur R. Colwell, Sr., M.D., Chicago
Moderator

Louis K. Alpert, M.D., Washington, D.C.
Bernard Becker, M.D., St. Louis
Forrest E. Kendall, Ph.D., New York
Philip M. LeCompte, M.D., Boston

MODERATOR COLWELL: I would like to introduce the members of this panel. Dr. Forrest E. Kendall is the Chief of the Biochemical Section of Goldwater Hospital and Professor of Biochemistry, College of Physicians and Surgeons, Columbia University.

Dr. LeCompte is Director of the Laboratories at the Faulkner Hospital in Boston and Clinical Assistant Professor of Pathology at Harvard Medical School.

Dr. Bernard Becker is Professor and Head of the Department of Ophthalmology, Washington University School of Medicine, St. Louis. Dr. Louis K. Alpert is Clinical Professor of Medicine, George Washington School of Medicine, Washington, D.C. I am Dr. Arthur R. Colwell, Sr., Professor and Chairman of the Department of Medicine at Northwestern University Medical School, Chicago.

We will discuss vascular disease, both in and out of diabetes, with emphasis on diabetes. Whereas the audience might hope that the panel will provide practical information, I fear that we will have very little to offer that can be applied. If anyone in the audience would like to supplement our discussion please raise your hand for recognition.

As you see, the panel is heavily weighted with men who have spent a great deal of time studying vascular disease at fundamental levels. In fact, it appears to many students of the disease that it is at such levels that practical knowledge will emerge. Our discussion, therefore, will lean towards fundamental mechanisms rather than practical applications.

In introduction each of us might spend a few minutes discussing a selected phase of this subject.

Dr. LeCompte, will you say a few words about some of the pathogenetic relationships between diabetes and its accompanying vascular disease?

DR. LECOMPTE: Thank you, Dr. Colwell. I should like to raise again the fundamental question that was touched on this morning by one or two of the speakers, namely, what is the relationship, if any, of the metabolic defect in diabetes to the vascular lesions.

When I say vascular lesions, I am referring now to the characteristic and perhaps pathognomonic capillary lesions in the kidney and in the eye. Incidentally, I think that when we say vascular disease with reference to diabetes, we should always specify what vessel we are talking about because the pathology and probably the pathogenesis of the various vascular lesions are quite different.

What I want to talk about is what Dr. Ricketts has discussed so well in some of his papers. You will recall that it was suggested that there are three possibilities. First, vascular disease might cause diabetes; second, diabetes might cause vascular disease; and third, both the diabetes and the vascular disease might be due to some common factor.

Dr. Ricketts has pointed out that there is not much evidence to go by on any of these possibilities. The first one I think is perhaps not widely held, with all due respect to Dr. Moschcowitz's interesting papers. The second one, that diabetes causes vascular disease,

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is, of course, very generally accepted and largely the basis for the rigid control that is exercised in some clinics. The third possibility is, as was indicated this morning, a distinct possibility.

It is quite conceivable, I think, that a hereditary factor may determine both the diabetic process and the vascular lesions. We have an example in Marfan's disease of a single gene influencing several different tissues, and including, incidentally, connective tissues of the blood vessel walls, including the mucopolysaccharides, which we think may be involved in the diabetic lesion. So it is entirely possible that the same gene may determine both the diabetes and the vascular lesion.

I should like to suggest that, although there is not much positive evidence for this hypothesis, there is not a great deal of evidence against it. One may cite as an example the fact that there are very few reported cases of these capillary lesions in diabetes due to some known cause, such as pancreatitis or hemochromatosis.

I have been unable to find in the literature, and I have been unable to find any one who knows about a case, verified at autopsy, of intercapillary glomerulosclerosis due to hemochromatosis or pancreatitis. Dr. Colwell, I would like to make a plea for the reporting of such cases because it seems to me that the evidence provided thereby is of tremendous importance. Perhaps somebody knows about such a case.

MODERATOR COLWELL: Dr. Kendall will next give us a few thoughts on the role of the lipoproteins in the pathogenesis of vascular disease.

DR. KENDALL: I accepted an invitation to participate in this discussion not because I had any competence in this field or any special knowledge of relationships between diabetes and atherosclerosis but because I believe that atherosclerosis, like diabetes, is a disease of metabolic origin. It is possible that the work on atherosclerosis may now be approaching a phase similar to the one that marked the discovery of insulin. About the only thing I can do is to state my point of view in connection with atherosclerosis.

I believe that the metabolic abnormality responsible for the occurrence of atherosclerotic lesions in the arteries of almost every adult member of our society is made manifest by high levels of beta-lipoproteins in the plasma. I believe that excessively high levels of beta-lipoproteins will lead to the development of lesions in normal arteries. I also believe that local damage to the arterial walls by other factors will lead to the development of atheromata in these sites at levels of beta-lipoprotein much lower than the levels required to produce lesions in normal vessels. These other factors may produce changes in the arterial walls but the lesions do not become atheromatous unless a sufficiently high level of beta-lipoprotein is present.

This concern with the lipoprotein levels rather than with serum cholesterol is a recent development beginning in 1950 with the work of Oncley and Gurd in the laboratories of the late Edwin Cohn in Boston, and with the work of Gofman and his co-workers in California. The special importance of the distribution of the serum lipids between the two fractions, the alpha- and the beta-lipoproteins, was first made evident by the work of Barr, Eder and Russ in 1951. Very little is known as yet about the metabolic processes that are involved in the building up and breaking down of the lipoproteins. We do not know much about the factors which are concerned in regulating their concentration in plasma. We do not know what special function the various lipoproteins may have beyond the obvious one of the transport of lipids from one part of the body to another. Our increasing knowledge of the composition of the lipoproteins has forced us to abandon our preoccupation with cholesterol metabolism and to consider the possibility that the metabolism of the protein, the phospholipid or the triglyceride moieties may also play a role in determining the serum lipoprotein level.

Even in infancy, human beings transport half of their cholesterol in the beta fraction and this percentage rises to 65 per cent in young women and to 75 per cent in young men. In both healthy men and women over 45 the percentage is around 80 per cent. In survivors of myocardial infarctions the percentage is still higher, averaging 87 per cent.

I think that it is highly significant that man, the only mammal in which atherosclerosis is a serious problem, is the only one that transports such a large proportion of his serum cholesterol in the beta-lipoprotein fraction. Dogs, rabbits, rats and all other mammals studied, transport much of their cholesterol in the alpha fraction. Damage to the arteries of these animals by mechanical injury or chemical agents does not result in the formation of atheromata unless the beta-lipoprotein in the serum is also raised. Raising the beta-lipoprotein in these animals to the values found in human beings leads to the formation of arterial lesions.

It seems that human beings have a metabolic pattern different from other animals which results in the maintenance of the beta-lipoproteins at a point where atherosclerosis tends to occur. This elevated lipoprotein level is not in itself a metabolic defect. The level of any component in the blood is determined not so much

by what is taking place in the blood, but by what is happening in the cells of the body. The defect lies in the inability of the peripheral cells to take up and utilize or store the lipids presented to them by the blood.

The effect of this defect may be aggravated by a plethoric diet, particularly one over-rich in fats. The defect may possibly arise from hormonal imbalance. Barr and others have shown that administration of estrogens may cause shifts from the beta to the alpha lipoprotein fractions, and androgens may cause shifts in the opposite direction. No one has yet been able to pinpoint the site or mode of action of these hormones. We do not know whether they act directly upon some enzyme system or whether they act by disturbing the general hormone balance of the whole body. Progress is being made in extending our knowledge of the enzyme systems involved in lipid metabolism.

MODERATOR COLWELL: Dr. Becker has done a good deal of experimental work with steroids in this field. He will introduce the subject of the relationship of adrenal cortical function to vascular disease.

DR. BECKER: Thank you, Dr. Colwell. Some six years ago a working hypothesis was formulated which implicated the adrenal cortex in the pathogenesis of the nephropathy and retinopathy of diabetes. I don't propose to review that hypothesis, but rather to attempt to bring it up to date very briefly with the aid of a few slides.

The glucocorticoid excretion of diabetic patients with and without retinopathy has been studied by Maengwyn-Davies and associates at the Johns Hopkins Hospital. A significantly increased excretion in the group with the retinopathy was demonstrated.

There are an increasing number of reports on adrenalectomy and hypophysectomy in the therapy of diabetic retinopathy. As best as I can judge, there are reported some thirty patients that have been subjected to each of these procedures. Several of these reports state that the progression of the retinopathy has been arrested. Unfortunately the choice of cases of this particular type of procedure has not been ideal for drawing such conclusions.

The experimental production of glomerular lesions by steroid administration continues to excite interest. You will recall that Dr. Rich presented a single case of a patient who was treated with ACTH and cortisone and developed lesions in the glomeruli which resembled the Kimmelstiel-Wilson lesion. This patient did not have diabetes. In addition there are a number of reports confirming Rich's findings of the production of lesions in rabbit glomeruli by injection of cortisone or other steroids. These lesions are not identical with Kimmelstiel-Wilson lesions, but bear a resemblance to them.

In addition I might remind you of the recent report from Boston by Sommers and Haley on the appearance of an ultraviolet absorption spectrum in the glomerulus of patients treated with cortisone which resembles the absorption spectra of the kidneys of patients with Kimmelstiel-Wilson disease. There are scattered reports of patients without diabetes receiving ACTH or cortisone for other conditions and developing capillary aneurysms in their retinas.

(At this point Dr. Becker showed slides which demonstrated some of the more startling examples of what he was discussing.) 1. Fundus photograph of a patient with capillary aneurysms treated for two years with ACTH and cortisone; 2. photograph of the appearance of the eyegrounds of another patient treated with steroids; in the region of the macula there were seen capillary aneurysms; 3. a slide demonstrating the appearance in a patient with pemphigus who had received cortisone therapy continuously at large doses up to 350 mg. per day for two years; he was seen with Dr. Marvin Rosecan; 4. a black and white photograph of a periodic acid fuchsin stain of the flat preparation of his retina. The lesions are quite apparent and there is a tremendous number of them. There are capillary aneurysms, both hyalinized and patent.

MODERATOR COLWELL: Dr. Alpert will open with a few minutes on the clinical management of complications of vascular disease in diabetes.

DR. ALPERT: With regard to the clinical management of the vascular complications, it might be worthwhile first to state clearly what we mean by that terminology. It is important to understand that therapeutically we are not dealing with the primary lesion in the vessel or capillary, but only with the results of the vascular obstruction. This statement is not as discouraging as it may seem, because a great deal can be accomplished in preventing the disastrous results of vascular obstruction. This is particularly true with respect to the lower extremities. The simple procedures involved in the care of the feet and the provision of properly fitted shoes are of greater importance than many physicians seem to appreciate. I may cite, as one example of this point of view, the fact that in the diabetic clinic with which I am associated, since we established a foot clinic staffed by orthopedists about ten years ago, we have not had to perform a single amputation.

MODERATOR COLWELL: Now we will have a question and answer period which should bring out more specific

discussion. First, a question on pathogenesis. What pathological differences and similarities are there between vascular disease in diabetics and nondiabetics? Dr. LeCompte.

DR. LECOMPTE: I think it is proper to say that as far as we know, there is no qualitative difference in diseases of the larger arteries between diabetics and nondiabetics.

First we have atherosclerosis, the familiar intimal thickening with deposition of fatty substances, which leads to coronary disease and so on. In so far as I am aware, there is no evidence that this disease differs *in kind* in the diabetic and in the nondiabetic. It often appears earlier and is often more severe in diabetes, strikingly so in diabetic females, but apparently the difference is quantitative and not qualitative.

Then we have medial calcification or so-called Mönckeberg's sclerosis, in which calcium is deposited in the muscular coat, chiefly in the vessels of the lower extremities. Here again, as far as I am aware, there is no difference in kind, although there is a striking quantitative difference. As you know, it appears in some of the young diabetics of long standing for reasons entirely unknown. Apparently it has nothing to do—nothing specifically, at any rate—with atherosclerosis.

Then we have diffuse intimal fibrosis, which is a recognized condition that increases with age. Some recent papers suggest it does have a relation to atherosclerosis. Here again it is found in diabetics, but looks just the same, and is the same as far as we know as in the nondiabetic.

There is arteriolar sclerosis, hyalinization and thickening of the arterioles, which is familiar, of course, as benign nephrosclerosis in hypertension. It is found in the diabetic, and again the difference seems to be quantitative. In the kidney it seems to involve the efferent arteriole of the glomerulus, which it usually does not in nondiabetics. There again it seems to be quantitative rather than qualitative.

Then finally we come to the capillary lesions which, of course, are characteristic of diabetes, and very possibly specific for it, certainly nearly so. By these we mean, of course, intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease, the nodular type, not the so-called diffuse type, and not the exudative type) and the retinal aneurysms which Dr. Becker has illustrated.

MODERATOR COLWELL: Dr. Alpert, what significant differences between vascular disease in diabetics and in nondiabetics do you see clinically? Is there any consistent time relationship between the diabetes and vascular disease?

DR. ALPERT: From a clinical standpoint, I would have to support what Dr. LeCompte has said regarding the pathological changes. The peripheral vascular lesions tend to develop earlier, and are quantitatively more severe and more extensive in the diabetic than in the nondiabetic. However, we have failed to find any qualitative differences in this respect. In other words, one can demonstrate identical types of cases in both groups. On the other hand, this does not apply to the capillary lesions. In this respect the distinction between the diabetic and nondiabetic is so great that one can, with a fair degree of assurance, make a presumptive diagnosis of diabetes when the capillary aneurysms are seen initially in the retina.

With regard to the kidneys, the problem is a little more difficult. However, needle biopsy of the kidney has helped us to detect some cases of glomerulosclerosis at an earlier stage than we were able to establish on purely clinical grounds.

MODERATOR COLWELL: Dr. Kendall, I have two related questions. Why are vascular complications relatively so much more common in diabetic than nondiabetic women as compared with men, and is vascular disease of hormonal origin?

DR. KENDALL: I think that there is a hormonal basis for the high beta-lipoprotein levels found in men as compared to women. I didn't think any one at the present time can pinpoint just what this hormonal basis consists of, but if it is important, you would expect it to be accentuated in diabetes, where you perhaps are superimposing other imbalances upon those referable to sex differences. I think that to explain why young diabetic women have more arteriosclerotic complications than young diabetic males, you would either have to ascribe it to a hormonal difference or to an environmental difference.

Is there a systematic difference in the environmental conditions confronting the diabetic men and diabetic women that could possibly play a role?

I am not at all certain that Dr. Levine's address that preceded this discussion may not give us a clue. At least theoretically men exercise more strenuously than women, and it can be that this greater exercise in men protects them to a certain extent from atherosclerotic complications in diabetes.

MODERATOR COLWELL: Dr. Becker, here are two questions concerning retinal lesions.

First, discuss the specificity of the capillary aneurysm in diabetes, and second, can the characteristic capillary lesions be produced experimentally?

DR. BECKER: As to the specificity, retinal vein oc-

clusions are associated with a number of capillary aneurysms peripheral to the site of the occlusion. The occlusion can be on an atherosclerotic basis or inflammatory basis. In addition, as we have demonstrated, one sees capillary aneurysms which we think are essentially identical with those seen in diabetic retinopathy in some few individuals who are treated with steroids. In a review of patients at Hopkins Hospital who died with untreated pernicious anemia, three out of twelve of these had capillary aneurysms in flat preparations of the retina. Therefore, the lesion is not entirely specific for diabetes. On the other hand, it is the commonest cause of this lesion as seen by the ophthalmologist.

As to the second question about whether they can be produced experimentally, we have seen very few capillary aneurysms with cortisone therapy in rabbits. The rabbit unfortunately has a very limited retinal vascular circulation. Actually our best experimental animal to date has been man. Although a rare complication, cortisone administration seems to produce lesions in man more readily than any other animal.

I might add that the renal lesions which are seen in a large percentage of cortisone-treated rabbits, have not been demonstrated in similar treatment of any other species.

MEMBER OF AUDIENCE: Dr. Becker, is there any remission of the capillary aneurysms after discontinuing cortisone therapy?

DR. BECKER: That is an important point. There is a remission and this convinces us that the retinopathy of diabetes can be reversed in its early stages. It is interesting to observe in patients who have been treated with cortisone and develop a capillary aneurysm what happens to that aneurysm clinically. It becomes hyalinized and turns from a red to a small white spot. When one reviews patients with diabetic retinopathy, one finds many such white spots which we believe to be the hyalinized capillary aneurysm.

MODERATOR COLWELL: How about the renal glomerulus in this connection?

DR. LECOMPTE: Regarding experimental reproduction in experimental animals, I should like to suggest the Kimmelstiel-Wilson lesion has not been accurately reproduced. As Dr. Ricketts says, you have to decide how close you are going to get to it, but I don't think that really anybody has gotten very close.

(The following remarks were illustrated with photomicrographs in color, representing human lesions stained by the periodic-acid Schiff method.)

The typical nodular lesions of intercapillary glomerulosclerosis appear as hyaline masses in the periphery of the glomerular tufts. There is also thickening of the basement membrane of the tubules, something emphasized by Dr. Kimmelstiel himself at a recent meeting in New York at The Mount Sinai Hospital, where he suggested that the hyaline material is deposited where epithelium and connective tissue come in contact. The thing I would like to stress is that a patent capillary passes over the glomerular nodule in the typical Kimmelstiel-Wilson lesion as seen in man.

There is another type of lesion which has appeared frequently in recent literature, and that is the so-called exudative lesion which may be associated with intercapillary glomerulosclerosis in diabetics. A homogenous acidophilic material is seen, sometimes in the lumen of a capillary, sometimes in an indefinite location. The so-called capsular drop is one of the manifestations of this so-called exudative lesion; it often appears to be attached to the capsule of Bowman and to lie within the capsular space. The homogenous eosinophilic material is often seen to be vacuolated and often seems to be intracapillary, i.e., in the lumen, quite unlike the typical nodular lesions mentioned before. To show that the exudative lesion is nonspecific, a slide is shown of the kidney of a nondiabetic who had a nephrotic syndrome associated with chronic glomerular nephritis. The lesions in diabetics and in nondiabetics are essentially indistinguishable. I am stressing this because I think it is this "exudative" lesion which the experimental lesion resembles.

The next is a slide kindly sent me by Dr. Arnold Rich. This is from one of his original rabbits in which the lesion was produced with cortisone. The hyaline material seems to be definitely inside a capillary, and indeed, most of them appear so to me. Also, Dr. Rich stated in the letter that he had never claimed that this was a reproduction of the Kimmelstiel-Wilson lesion, but simply that there was some resemblance. What I should like to emphasize again is that the material is inside the capillary, hence unlike the nodular lesion, which has a free capillary running over its surface. Dr. Rich also sent a slide of the kidney of a patient treated with ACTH which showed similar lesions, but again not a typical nodular lesion.

(Dr. LeCompte showed a slide demonstrating the lesions in the kidney of a rabbit treated with cortisone.) There is a mass in the capillary with red blood cells in the center of the hyaline material. As Drs. Bloodworth and Hamwi have pointed out, this resembles the exudative lesion which we have been talking about, which is generally agreed to be nonspecific. It does not reproduce the classical Kimmelstiel-Wilson lesion in the

diabetic. A similar lesion produced in Dr. Marble's laboratory is shown with the PAS stain showing that the hyaline substance contains considerable carbohydrate.

What I want to emphasize is that this experimental lesion does not reproduce the Kimmelstiel-Wilson disease that we see in the human. I should also like to suggest that the experimental one may well be a cortisone effect, and that when we do find the "exudative" lesion in the human, it may be the result of a nonspecific stress situation. In other words, it may be due to adrenal cortical activity, but may have nothing at all to do with diabetes.

As to the retinal lesions, I leave those up to Dr. Becker. So far as I know, he is the only one who has successfully produced them in the experimental animal. I think his human experiment was most striking and dramatic, but would suggest that it is still possible this patient could have had the hereditary factor for diabetes, and that the cortisone could have acted as a precipitating factor.

MODERATOR COLWELL: Drs. Bloodworth and Hamwi, do you want to add anything to the discussion about glomerular lesions?

DR. JAMES M. B. BLOODWORTH, JR.: We are in general agreement, I think, on every point, and we feel certain it is similar to the action of cortisone. Other than that, you draw your own conclusions.

MODERATOR COLWELL: Dr. Becker, why don't we see diabetic retinopathy in severe long-standing Cushing's syndrome?

DR. BECKER: This has been the embarrassing question asked every time we have presented the adrenal hypothesis. There are several possible answers, but none entirely satisfactory.

It is true that capillary aneurysms are seen in long-standing Cushing's syndrome, but usually only in those that have diabetes of long standing does the question arise as to whether there is an abnormal steroid, or an abnormal way of handling a steroid that produces the retinal lesions in the diabetic. It may not be merely an increased adrenal cortical function but qualitative as well as quantitative alterations in steroids. The fact that it takes more than just increased cortisone is evidenced by the rarity of experimental production in humans in spite of the vast amount of cortisone used.

MODERATOR COLWELL: Dr. Root has used the term "diabetic triopathy." Dr. Becker, please discuss the relationship between diabetic retinopathy, neuropathy and nephropathy.

DR. BECKER: In 1952 we reviewed a large series of histories at Hopkins with a diagnosis of diabetic neuropathy. Of these some forty-eight patients had adequate eye examinations, and well over 90 per cent of them had retinopathy. Therefore, in incidence the retinopathy and the neuropathy correlate. I think that has been other people's experience.

The other question about the relationship of retinopathy to neuropathy, Friedenwald and Day and Ashton have studied histologically the kidneys of diabetic patients at autopsy. When the same patients were classified on the basis of flat preparations of the retina into a retinopathy group and nonretinopathy group, there was no instance of nephropathy occurring in the absence of retinopathy.

In the retinopathy group there was some 60 per cent incidence of nephropathy, but this incidence could be raised if serial sections of kidneys were studied.

The best estimate I can give at present is that something close to 80 to 90 per cent of all patients who have retinopathy as demonstrated by flat preparations of the retina will have Kimmelstiel-Wilson lesions in the kidney at autopsy.

MODERATOR COLWELL: Dr. Alpert, is there any relation between arterial or venous pressure and the development of vascular lesions?

DR. ALPERT: I would like to take the short end of that question first, regarding venous pressure. I know of no relationship between venous pressure and vascular lesions.

With regard to the arterial lesions, it is my opinion that they have a definite relationship with elevated arterial pressure. The retinal hemorrhages which are secondary to the capillary aneurysms are usually more severe and more progressive in the diabetic who also has hypertension, than in the one who does not. Furthermore, the management of the hypertension with the currently available hypotensive agents has, in many instances, been associated with pronounced reduction in the severity of the retinal hemorrhages. This represents another of the important preventive aspects of the complications of diabetes.

MODERATOR COLWELL: I have always wondered whether these characteristic capillary lesions are found elsewhere in the body than in the retina and kidney, and if not, why not? Does anybody know? Dr. LeCompte, have you found them elsewhere?

DR. LECOMPTE: No, I haven't. I think the methods for looking for them are a bit difficult. We have made some attempts. The only thing I can suggest is that the retinal and the renal capillaries have the highest capillary pressure in the body, and that this may perhaps have something to do with the lesions appearing

in the kidney, and in the retina.

MODERATOR COLWELL: Here is a question from the audience for Dr. Kendall. How about the report at the International Cardiac Congress two years ago that a high fat diet was associated with a high rate of cardiac deaths with arteriosclerosis?

DR. KENDALL: I want to point out that this statement is based upon epidemiological information. It is possible to show that a high rate of cardiac deaths in arteriosclerosis is associated with such diverse factors as age, race, occupation, diet, concurrent disease. This list could be extended to cover at least fifteen or twenty different factors that have been shown by this type of stress to be associated with an increased incidence of cardiac death.

Now, of course, the difficulty in all this epidemiological research is to be sure that you have isolated the one factor, to be sure that the factor that you are studying is the only systematic difference between your populations.

Of course, no survey that has been made up to the present time meets this criterion. You can find other factors in the population study that are systematically present throughout the population, and I do not consider at this point that high fat diets are associated with a high rate of cardiac death has been proved today. The possibility has been raised, but it has not yet been established.

MODERATOR COLWELL: One final question on pathogenesis. Are serum mucopolysaccharides related to the development of vascular lesions, Dr. LeCompte?

DR. LECOMPTE: I can't answer because I don't know. The reason for estimating serum mucopolysaccharides is that the diseases we are interested in have to do with the ground substance and basement membrane which have become popular since the original publication of Gersh and Catchpole, the ideas of which were applied so brilliantly in diabetes by the late Dr. Friedenwald, with the help of Dr. Becker. But I should like to emphasize that we know very little about the basic physiology and metabolism of this ground substance, this mysterious gel, which holds cells together, and makes up basement membranes. It does a lot of strange things. It changes with aging, as shown in a paper of Dr. Sommers which is soon to appear. It is involved in many diseases such as the collagen diseases.

All I should like to suggest is that we know so little about this substance that the interpretation of levels of serum mucopolysaccharides is fraught with great difficulty, and it is especially difficult to tell whether an increase, for instance, in the level of those substances may not be secondary to disease involving the connective tissue rather than having any primary etiological significance.

MODERATOR COLWELL: We have used almost all of our time on pathogenesis. Dr. Becker, do you know of anything effective in the therapy of retinopathy?

DR. BECKER: No, I don't. I am sorry.

MODERATOR COLWELL: Does anyone wish to discuss the relationship between control of diabetes and the development of vascular complications? This was quite thoroughly discussed this morning, I think, so perhaps we should spend no more time on it.

We will now close the panel. I want to thank the panelists for their discussion and the audience for your attention.

Metabolic Regulation by Kinetic Responses and by Metabolic Adaptations

It appears probable that metabolic systems with constant amounts of enzyme can vary somewhat in reaction rates under physiological conditions. These kinetic responses probably play some role in momentary adjustments of metabolic rates before metabolic adaptations of the amounts of enzyme proteins have time to occur. Such a role has been looked for most intensively as the mode of hormone action. No acceptable instances of this kind of hormone action have been found, nor has it been shown how hormones could affect the rates of enzyme reactions without affecting enzyme concentration. On the other hand, many hormones and numerous other factors do alter the amounts of enzymes in the tissues in specific manners. These concentration changes, by whatever mechanism they occur, can potentially alter metabolic reactions, and thus provide a means for the regulation of metabolism.

From "Enzymatic and Metabolic Adaptations in Animals" by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* 36:164-254, 1956.

Recent Statistics on Diabetes

The death rate from diabetes in the first nine months of 1956 shows a moderate increase over the figures for the corresponding period of 1955. Provisional figures for the United States, based upon a 10 per cent sample of the death certificates, indicate an increase of about 5 per cent. The reasons for this small increase are not readily apparent. General health conditions have been relatively good, but despite the relative absence of any widespread outbreak of respiratory disease, the death rate from pneumonia has been somewhat higher thus far in 1956 than in the same period of 1955, and there may have been a parallel increase in mortality among diabetics from this cause. Some of the increase in diabetes mortality may reflect the continuing increase in the proportion of older persons in the population.

The recent trend of mortality in the cities and states from which reports are received regularly is not uniform (table 1). New York State, New York City and Philadelphia show lowered rates for the first nine months of 1956 as compared with 1955, whereas Maryland, Baltimore and Boston show increases. The figures for the two Canadian cities show opposite trends. The rate for Toronto was appreciably higher in 1956 than in 1955, whereas the reverse was true in Montreal.

In England the figures for London Administrative County were about the same for the first nine months of 1955 and 1956. Data for the country as a whole, available for only the first half of the year, show a decline, much greater for females than for males.

Regional data for the United States based upon the 10 per cent sample, for the first nine months of 1956, show that in most areas the death rates from diabetes in the first nine months of 1956 were generally higher than in the same period of 1955, and 1954. The major exception to the general pattern of changes between 1955 and 1956 was the West South Central States. There the rate this year was much lower than in 1955. In the South Atlantic and the Pacific States moderate decreases were recorded (table 2).

Detailed figures on diabetes mortality by color, sex and age for the United States are now available for the year 1954 and are shown in table 3. Among white persons the death rates were less than 1 per 100,000 up to age fifteen and among white males at fifteen to nineteen. The main features of this table in addition to the general rise with age in the rates in all race and sex groups are these: The rates declined at the very advanced ages. The maximum rate among whites in 1954 was recorded at ages eighty to eighty-four, among colored males at seventy-five to seventy-nine and among colored females at seventy to seventy-four. Among whites the rates for females exceeded those for males during the teen-ages, but between ages twenty and fifty, the male rates were the higher, with the maximum difference recorded at ages forty to forty-four. Thereafter the rates for white females were in excess of those for white males. Relatively the difference was at its peak between the ages of sixty-five to sixty-nine when the female rate was about two-thirds higher than the male rate.

Among the nonwhites the rates among females were higher than among the males with but few exceptions, primarily at the earlier ages where the numbers of deaths were small and subject to relatively large variation from year to year. As in the whites, the rate for late teen-age colored girls was higher than in the boys. In some age groups the rate among colored women was more than double that among the men. The death rates for colored persons were generally appreciably above those for whites at adult ages up to seventy. Between ages thirty-five and sixty the rates for colored women were several times as high as those among white women. At ages seventy to seventy-four the rates for females were approximately the same in whites and nonwhites; otherwise the rates in old age were higher among the whites.

Table 4 gives the 1955 mortality data in detail by color, sex and age among urban wage-earning families insured in the Metropolitan Life Insurance Company. Much the same characteristics were found as in the population for the country. The excess of the death rate at the older ages among women, as compared with men, was somewhat greater in the insured group than in the general population.

A recent review by Burchell and Berkson of the experience with cardiac deaths occurring in the hospitals of Rochester, Minnesota, shows clearly the proneness of diabetics to early death from coronary heart disease (table

Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual materials suitable for this section in future issues from Association members and other readers of the Journal.

TABLE 1

Recent data on diabetes mortality
Deaths and death rates—January-September 1956 and 1955

Area	Death rates per 100,000		Number of deaths	
	1956	1955	1956	1955
United States (10% sample)	15.9	15.2	1,973	1,869
Metropolitan Life Ins. Co.				
Industrial policyholders	15.2	15.1	2,024	2,041
New York State	19.6	19.9	2,377	2,375
New York City	19.2	20.8	1,165	1,250
Maryland	19.1	16.3	397	331
Baltimore	26.1	21.0	189	152
Boston	16.9	15.2	104	92
Philadelphia, resident	18.8	21.9	306	356
Toronto	19.4	15.4	99	78
Montreal, resident	14.1	15.9	116	129
London (Administrative County)	8.3	8.2	205	203
	Jan.-June		Jan.-June	
England and Wales				
Total	7.7	8.3	1,714	1,839
Males	5.6	5.8	601	622
Females	9.6	10.6	1,113	1,217

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in "Current Mortality Analysis," a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geographic division;
United States reporting area for the 10 per cent sample;
January-September 1956, 1955 and 1954

Geographic division	Death rates per 100,000*			Number of deaths*		
	1956	1955	1954	1956	1955	1954
U. S. reporting area	15.9	15.2	15.3	1,973	1,869	1,830
New England	18.8	18.1	16.7	137	130	122
Middle Atlantic	21.7	20.9	20.7	530	504	497
East North Central	19.9	18.7	17.6	510	469	432
West North Central	15.5	12.1	14.9	175	134	162
South Atlantic	11.5	12.1	12.9	207	213	220
East South Central	12.4	9.1	11.1	109	79	95
West South Central	9.5	12.6	11.2	114	148	128
Mountain	12.4	9.7	6.8	57	43	29
Pacific	10.0	11.2	11.9	134	149	145

*Excludes armed forces overseas.
Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."
Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

5). This study covered all cases where a cardiac diagnosis was registered, exclusive of postoperative deaths and children under fourteen years of age. Of the twenty-seven deaths from coronary disease among diabetics, four or nearly 15 per cent occurred at ages twenty to fifty, as compared with only seven out of 178 deaths or 3.9 per cent among nondiabetics. Only seven or about one-fourth of the coronary deaths among diabetics occurred at ages seventy and over as compared with almost 45 per cent among the nondiabetics. The mean age at death of the diabetics dying from coronary heart disease was about sixty-two years as compared with sixty-eight among the nondiabetics. Diabetics accounted for 13 per cent of all coronary deaths as compared with only 5 per cent of the deaths from other forms of heart disease.

The 1950 amendments to the Social Security Act included Federal participation in assistance payments to needy persons who are permanently and totally disabled. In October 1950, sixteen states had developed plans and made payments under the new program and by June 1951, thirty-one states were making such payments. For administrative reasons it was necessary to obtain certain information about the social and medical characteristics of the recipients. Consequently, some information is

TABLE 3

Number of deaths and death rates per 100,000 from diabetes mellitus by race, sex and age. United States, 1954. Excludes Armed Forces overseas.

Age period (Years)	Death rates					Deaths				
		White		Nonwhite			White		Nonwhite	
	Total	Male	Female	Male	Female	Total	Male	Female	Male	Female
All ages	15.6	12.7	18.8	9.8	18.1	25,151	9,009	13,705	826	1,611
Under 1	0.5	0.5	0.3	0.9	1.3	18	8	5	2	3
1-4	0.3	0.3	0.3	0.6	0.2	44	18	18	6	2
5-9	0.3	0.3	0.3	0.6	0.1	49	19	23	6	1
10-14	0.6	0.5	0.6	1.0	0.9	75	26	34	8	7
15-19	0.8	0.5	1.0	1.3	2.0	92	23	46	9	14
20-24	1.2	1.3	1.0	1.8	1.1	121	55	49	10	7
25-29	1.9	2.3	1.5	2.4	2.4	228	117	80	14	17
30-34	2.4	2.6	2.0	3.5	3.5	298	141	112	21	24
35-39	3.2	3.6	2.3	5.3	6.1	367	182	120	28	37
40-44	4.7	5.0	2.9	8.2	14.7	518	242	144	44	88
45-49	7.6	7.0	5.5	12.9	27.9	752	311	246	60	135
50-54	15.4	12.6	13.3	21.3	56.3	1,338	490	528	86	234
55-59	28.3	21.3	30.3	28.0	81.3	2,188	742	1,095	90	261
60-64	50.2	37.5	59.0	51.5	91.4	3,302	1,117	1,837	124	224
65-69	81.6	60.1	100.5	63.5	116.2	4,295	1,428	2,546	113	208
70-74	112.7	88.8	134.2	75.4	135.8	4,485	1,531	2,670	98	186
75-79	148.0	127.0	172.1	81.8	106.3	3,606	1,312	2,146	63	85
80-84	173.4	156.8	197.9	57.5	95.2	2,234	831	1,340	23	40
85+	149.3	146.1	163.9	66.7	89.7	1,132	415	662	20	35
Not stated						9	1	4	1	3

Source: United States Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics Special Reports—National Summaries, volume 44, number 12, Sept. 14, 1956.

TABLE 4

Death rates per 100,000 from diabetes mellitus by race, sex, and age periods. Metropolitan Life Insurance Company, Industrial Department, weekly and monthly combined, 1955.

Age period (years)	Total persons	White		Nonwhite	
		Male	Female	Male	Female
1 to 74*	8.1	6.4	9.5	7.0	12.2
1-4	0.7	0.6	1.0	—	—
5-14	0.3	0.2	0.4	—	—
15-24	0.8	0.3	1.0	0.7	2.4
25-34	1.7	1.7	1.6	3.6	1.0
35-44	3.4	4.6	2.0	7.8	5.9
45-54	11.6	10.9	9.0	11.2	27.5
55-64	45.1	28.6	51.4	42.5	60.5
65-74	110.9	74.0	132.7	46.7	132.2

*Standardized for age, standard million of England and Wales, 1901.

available on persons receiving assistance because of disability from diabetes from the study made under the auspices of the Bureau of Public Assistance of the Social Security Administration. When the study was made, in the early summer of 1951, over 90,000 disabled persons had been found eligible for assistance. The study was conducted on a sample basis, and consequently, the figures presented here are primarily estimates. While thirty states are represented in the study,

TABLE 5

Cardiac deaths in Rochester (Minnesota) hospitals, 1952-1953

A. Age distribution of patients who died with coronary disease, diabetic and nondiabetic separately

Age group	Diabetic		Nondiabetic	
	Number	Per cent	Number	Per cent
Total	27	100.0	178	100.0
20-29	1	3.7	—	—
30-39	1	3.7	2	1.1
40-49	2	7.4	5	2.8
50-59	6	22.2	35	19.7
60-69	10	37.1	58	32.6
70-79	6	22.2	57	32.0
80+	1	3.7	21	11.8
Mean age, years	61.7		67.7	

B. Incidence of diabetes among cases of coronary heart disease compared with other heart disease

Disease group	Total	Diabetes	
		Number	Per cent
Total	323	33	10.2
Coronary heart disease	205	27	13.2
Other heart diseases	118	6	5.1

Note: All cases for whom a cardiac diagnosis was registered. All postoperative deaths and children (under 14 years of age) were excluded.

Source: Burchell, H. B., and Berkson, J.: Review of Medical Cardiac Deaths; Rochester Hospitals, 1952-1953. Proceedings of the Staff Meetings of the Mayo Clinic, vol. 31, no. 4, Feb. 22, 1956.

TABLE 6

Diabetes as a major impairment among recipients of aid to the permanently and totally disabled, 30 states, mid-1951

A. By age, race and sex

Race and sex	Total	Under 35	35-54	55 & over
		Total number of recipients		
Total	93,359	9,285	33,971	50,103
White	64,397	6,290	21,904	36,203
Nonwhite	28,962	2,995	12,067	13,900
Male	46,480	5,158	17,731	23,591
Female	46,879	4,127	16,240	26,512
		Per cent diabetes of total recipients		
Total	2.1	.6	1.6	2.7
White	1.9	.6	1.1	2.7
Nonwhite	2.5	.8*	2.7	2.7
Male	1.2	.9	.9	1.5
Female	3.0	.2*	2.4	3.8

*Estimated

B. By mobility status

Mobility	Total number of recipients	Per cent diabetes of total
Total	93,359	2.1
Household		
Total	19,350	2.4
Bedridden	5,313	1.5
Chairfast	5,829	2.6
Other	8,208	2.8
Capable of activity outside home		
Total	73,973	2.0
With help of another person	7,272	1.7
With help of a device	7,198	1.7
By self	59,503	2.1

C. By duration

Years	Per cent (estimated) Total	Total reported
Total	100.0	100.0
Under 1	3.2	3.9
1 to 2	5.4	6.7
2 to 5	21.2	26.4
5 to 10	17.8	22.1
10 or more	32.9	40.9
Not reported	19.4	—

Source: Characteristics of Recipients of Aid to the Permanently and Totally Disabled, Mid-1951. Public Assistance Report No. 22. U. S. Dept. of Health, Education and Welfare; Social Security Administration, Bureau of Public Assistance. Washington, D. C., April 1953.

the volume of assistance payments is relatively much higher in the Southern States than in the other parts of the country, and consequently, the proportion of Negroes in this experience is relatively large. It should be clearly understood that the group under consideration is a very special one, consisting primarily of persons who are both indigent and disabled.

Data relating to diabetics in this study are summarized in table 6. The figures relate to cases in which diabetes was reported as the most seriously disabling impairment. Diabetics accounted for 2.1 per cent of the total disabled. The proportion of diabetics increased from 0.6 per cent at ages under thirty-five to 2.7 per cent at ages fifty-five and over. The percentages at ages under fifty-five were higher among nonwhites than among white recipients of aid. At ages fifty-five and over the proportions were similar. Even greater contrast was found in the sex ratios. At all ages the proportion for females was 2½ times that for males.

It is noteworthy that most of these diabetics had complications or other impairments. Thus, the proportion with multiple diagnoses was nearly 85 per cent as compared with less than 60 per cent of those disabled for nondiabetic conditions. Most of these diabetics had the disease for five years or more. Such cases accounted for 89 per cent of the total in which the duration of the disease was reported.

In view of the higher average age of the diabetics and their higher frequency of complications as compared with nondiabetics in this experience, it is not surprising that they contributed a somewhat higher percentage of the housebound than of cases capable of activity outside the house. Nevertheless, the proportion of the housebound diabetics who were bedridden was less than that for the housebound with all other diagnoses combined. Of the diabetics who were not housebound the proportion requiring help, either personal or mechanical, to get around, was less than in the nondiabetic disabled.

EDITORIALS

CANADIAN AND BRITISH EXPERIENCES WITH THE SULFONYLUREAS*

The *Canadian Medical Association Journal* of June 15, 1956,[1-19] and the *British Medical Journal* of Aug. 24, 1956,[20-26] are largely devoted to studies of the new oral hypoglycemic agents. In view of the fact that final evaluation of these drugs cannot be made until more is known about their mode of action, it is fitting that the leading article in each journal has been written by a basic scientist, one the Canadian physiologist, Charles H. Best, and the other the English biochemist, F. G. Young.

Therapeutic Effects

In connection with any new treatment for diabetes, it must be pointed out that, while outpatient trials are valuable and necessary, unassailable conclusions can be drawn only from studies carried out on hospitalized patients under rigidly controlled conditions with pre- and post-experimental periods of sufficient length, usually weeks rather than days; and even in these circumstances judgment is often difficult. The time consuming and expensive nature of such observations accounts for their scarcity. Some Canadian and British physicians have had the opportunity to conduct carefully planned investigations on inpatients, while the majority, as is true in all countries, have had to be content with office or clinic material or brief hospitalization. One has the impression that the wise precaution of using placebos during the control periods has been more widely employed in Britain than on this continent.

Taken together, the two series report a total of 245 diabetic patients, of whom all but six were treated with carbutamide (BZ-55). The majority were chosen for their probably favorable response. In judging therapeutic results it is necessary to omit thirty-three patients, some of whom were children, and others of whom had interfering complications or were insufficiently studied. Of the remaining 212, a definite reduction of hyperglycemia and glycosuria, although not always to normal, was noted in 144, or 68 per cent. Because of differences in experimental design and criteria of control it is difficult to make a positive statement on an important point, namely, in what percentage of older, milder diabetics who nevertheless required insulin was it possible to keep the two-hour postprandial blood sugar below, say, 150 mg. per 100 ml. with carbutamide alone, a feat that is relatively easy to accomplish with insulin? The data would indicate that certainly less than 68 per cent, and probably less than 50 per cent, could be so controlled.

There is confirmation of the fact that the sulfonylureas are in general ineffective in patients whose disease began at a young age, who require large amounts of insulin, and who lapse into ketosis readily. These patients, as Wrenshall[5] points out, are largely those who have little or no extractable pancreatic insulin. In contrast to the earlier German reports, three English groups[22, 23, 24] find that the response of patients to carbutamide is not related to the duration of diabetes; two of them find no relationship to body weight and one no correlation with the duration of insulin therapy or with present age. Single dose tests seemed to have limited value in predicting a favorable long-term response.

Toxicity

The average maintenance dose was from 1 to 2 gm. daily. Among the 245 patients who received the drug, 37, or 15 per cent, experienced side reactions of one sort or another. Most of these were of a minor nature, consisting of skin rash, fever, giddiness and gastrointestinal disturbance. In some cases a rash which had appeared during treatment with carbutamide disappeared gradually when tolbutamide was substituted, while in others it subsided even during continued treatment with carbutamide. One author[21] reports that granulocytopenia was the rule during the first two weeks of treatment, the neutrophiles returning to normal in some cases despite continued treatment but persisting at low levels in others. Several patients with thrombocytopenia have been observed, three[21, 23] with frank purpura, including one with a platelet count of 60,000 per cu. mm.

Thyroidal uptake of I^{131} was diminished in the first two weeks of treatment in six patients so tested[21] but returned to normal while the drug was still being taken. One patient being treated for myxedema experienced an increase in her requirement for thyroid,[21] and in another patient hypothyroidism occurred for the first time while he was receiving carbutamide.[25]

* The intention in this review is to summarize interpretively the contributions in two specific journals. Reference to other investigations is not complete and will be made only when immediately relevant or necessary to round out the subject.

No instances of jaundice are mentioned and there were no deaths.

The incidence of toxic reactions in these studies is two to three times that observed for carbutamide in this country.[27] The reasons for the difference are not clear. The lack of deaths is not as reassuring as it might seem. If the American experience showing approximately 0.1 per cent mortality[27] is any guide, 1,000 patients would have to be treated before one fatality could be expected.

Place of Sulfonylureas in Therapy

In these reports, conclusions as to the usefulness of the drugs are dominated by conservatism. While there were some patients in whom demonstrably needed insulin could be replaced by orally administered preparations, the majority of those who responded favorably could be managed with diet alone. Many authors are impressed by the toxic potential of the compounds and regard lack of knowledge of their mode of action as a deterrent to their general application. Walker[25] expresses the consensus thus: "The hypoglycaemic sulphonamides would seem to be indicated in only a comparatively small group. Until their value has been proved and their possible hazards more fully explored they cannot be recommended for widespread use."

Mechanism of Action

There is agreement that the sulfonylureas are ineffective in the known (depancreatized dog)[2, 3] or presumed (growth-onset diabetes in man)[17, 19, 22, 23] absence of insulin. Therefore they do not act as insulin does. There remain, so far as insulin is concerned, the questions of whether its secretion is stimulated when the pancreas is present and functioning to some degree, and whether the action of whatever insulin is available, either endogenous or injected, is potentiated.

Respecting the possibility of secretory stimulation, Ashworth and Haist[8] have shown that the weight of islet tissue in rats fed carbutamide is increased over that of controls. Also favoring this hypothesis are experiments in dogs utilizing direct perfusion of the pancreas[28] and cross circulation.[29, 30] On the other hand, that the pancreas is not essential for the hypoglycemic action of the drugs is demonstrated by the fact that some totally depancreatized dogs maintained on suboptimal amounts of insulin experience a definite lowering of blood and urine glucose when treated chronically with carbutamide.[2, 3] These observations of course exclude suppression of the alpha cells and their postulated product, glucagon, under the prevailing conditions. They are compatible with, although do not prove, a potentiation of the injected insulin, but they are also compatible with an effect on other tissues (e.g., liver) for which a minimum of insulin may be necessary. The ability of carbutamide to reduce the blood sugar or insulin requirement in the depancreatized animal maintained with insulin is inconsistent with its usual failure to do so in the juvenile diabetic patient.[17, 23, 26] It should be noted also that in *acute* experiments on pancreatectomized man[31] and dog[32] no potentiation of injected insulin has been demonstrated.

If the action of the sulfonamides were either to stimulate the secretion of insulin or increase its effectiveness, it would be expected that the results of their administration would be essentially the same as if insulin itself were given. The Canadian and British scientists have added to the evidence that, aside from reduction of blood sugar and increase of liver glycogen, this is not the case. They have shown, as have others, that carbutamide does not augment the uptake of glucose or the formation of glycogen in the isolated rat diaphragm,[4] and in diabetic patients does not increase the arteriovenous blood sugar difference,[23, 24] diminish the rise of blood sugar after meals,[17, 21, 22] or alter the shape of the glucose tolerance curve.[21] The blood sugar value most affected is the fasting one, and when decreased postprandial values are observed they may be traceable to the lower starting levels. Thus, it appears that carbutamide has its greatest effect on endogenous carbohydrate metabolism and little if any on the rate of disposal of ingested or injected sugar, particularly so far as muscle is concerned. There is general agreement that it does not ameliorate the ketosis of insulin deficiency, although Kinsell[33] has reported that it reduced a diet-induced hyperketonemia in a nonacidotic diabetic patient.

Other comparisons with insulin may be mentioned. Duncan[21] states that sixteen patients who were responsive to carbutamide, studied for over twenty days, showed an average reduction in daily nitrogen excretion of 2.1 gm., whereas an unresponsive group showed no change. American investigators,[34, 35, 36, 37] however, have found no effect on nitrogen balance, and the preponderance of evidence is in their favor. Some of the latter,[31, 34, 35, 38] moreover, have demonstrated in diabetic patients that the sulfonylureas do not produce the rise in blood pyruvate and lactate or the fall in serum phosphorus and potassium that is regularly obtained with insulin. The respiratory quotient seems to have received scant attention.

The action of these compounds on the liver has been studied extensively, but with varying results. Clarke[4] reports that when added to rabbit liver slices in vitro

they diminish the output of glucose, the uptake of oxygen and the activity of cytochrome oxidase. Confirmation of reduced glucose output is provided by studies on the intact liver of man[39] and dog.[41] However, Berthet, Sutherland and Makman[42] have found that, while Orinase does inhibit the production of glucose by rabbit liver slices, the concentrations required are considerably greater than the plasma levels necessary for in vivo effects on the blood sugar. Ashmore[43] and his colleagues have reported no effect of the sulfonylureas on the appearance of glucose or disappearance of glycogen in liver slice preparations.

If the drugs did suppress hepatic glycogenolysis, a likely locus of action would be glucose-6-phosphatase. Hawkins[6] adduces evidence that the activity of this enzyme is diminished in liver homogenates from normal rats fed for three weeks on carbutamide. American workers, however, have reported either no effect[42, 44] or a slight effect[43] with high, not low, concentrations of the drugs when they were added to liver homogenates in vitro. After single parenteral doses that produced hypoglycemia in living rats the glucose-6-phosphatase activity of the liver was normal,[43] suggesting that the reduction of blood sugar was caused by something other than changes in this enzyme.

Reports of the influence of the sulfonamides on the glucagon-and adrenalin-induced release of glucose from the liver do not appear in the two journals here reviewed. In this country Vaughan[45] has found in liver slices that the compounds inhibit increased glucose production normally caused by these glycogenolytic agents, but there is abundant evidence that this effect is not obtained in the living organism.[35, 36, 38, 39, 42, 46-48]

Sirek's[2] finding that the pituitary is not necessary for the hypoglycemic action of the drugs is in agreement with the observations of others,[31, 34, 47, 49, 50, 51] who have also shown that the adrenal is not essential.

The demonstration by Friedlich[7] that carbutamide interferes with glucose absorption in the rat is interesting, but admittedly it is not sufficient to explain the lowering of blood sugar, especially in view of the fact that this effect is exerted chiefly on the fasting levels.

Finally, Young[30] makes an interesting suggestion. He points out that certain guanidine derivatives, acridine, sulfonamides and penicillin all have some hypoglycemic as well as antimicrobial properties. Recalling the finding of Markowitz and Rappaport (Physiol. Rev. *31*:188, 1951) that penicillin prevents the usually fatal outcome of hepatic artery ligation in dogs, and the further fact that the liver of many species normally contains anaerobic bacteria which may account for death in such dogs when untreated, he postulates that the sulfonylureas may act by inhibiting certain flora of the liver that normally destroy insulin. While this might explain the action of carbutamide, it would not clarify that of tolbutamide, and Young suggests that metabolic derivatives of the latter may be bacteriostatic whereas the parent substance is not. There is much evidence, however, to indicate that inhibition of insulin degradation is not the only way, if indeed it is a way at all, in which the sulfonylureas exert their hypoglycemic effect.

SUMMARY

British and Canadian experience with the sulfonylureas is in agreement with that of others that these compounds are inoperative in patients who experience ketosis readily with deprivation of insulin and are most effective in older patients with mild diabetes. Of these, the group in which the established need for insulin can be fully met by the sulfonamides is probably not large. Evidence is presented that, contrary to earlier reports, response is not related to body weight or to duration of diabetes or insulin treatment. The over-all incidence of side effects has been 15 per cent. Most of these were not serious, but disturbing hematologic disturbances were encountered in some cases.

It has not been possible to prove that any single organ or biochemical system is the sole site of action of these substances. The only solid fact is that the presence of insulin is essential. A number of possibilities have been excluded. Apparently the drugs do not facilitate the peripheral utilization of glucose even when insulin is available. They lower the blood sugar in the absence of the pituitary, the adrenals and the pancreatic alpha cells, and even in the absence of the beta cells when insulin is injected; but this does not necessarily mean that they have no effect on these tissues in the intact organism, and for the pancreas at least this remains a distinct possibility. Some effect on the liver seems established, if only because some toxic reactions are traceable to that organ, but the physiologic and chemical mechanisms involved are still unclear. It is not likely that the moderate suppression of thyroid function or intestinal absorption is sufficient to account for the reduction of blood sugar levels. Future investigations may well show that the sulfonylureas have multiple actions in the body.

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THE ORAL HYPOGLYCEMIC SULFONYLUREA COMPOUNDS

The Editors of this Journal have viewed with great interest the developing knowledge concerning the hypoglycemic sulfonylurea compounds. The mechanism of their action is not yet clear in man or laboratory animals and much controversial evidence has been accumulated concerning a role in stimulating pancreatic secretion of insulin and the potentiation of exogenous insulin even in the pancreatectomized subject. The need for long-term studies, including the search for remote toxicologic effects in experimental diabetes and human diabetes seems self-evident. All physicians hope for a cure as well as protective action in diabetics against some of the ophthalmic, cardiorenal and neurologic complications. This will require years of testing for adequate appraisal.

Meanwhile we question the wisdom of widespread clinical administration of the sulfonylurea drugs except under rigidly controlled conditions followed by careful evaluation. The well-known ameliorative effect of merely having diabetic patients report more frequently and more regularly to their physicians makes evaluation of therapeutic results in ambulatory patients difficult. Reduced glucosuria and a return to "normoglycemic" blood levels may follow food restriction incident to drug administration, or without it, if patients add a little more care and are reassured.

Duncan and others both here and abroad have noted even in those patients who initially respond favorably to the oral hypoglycemic compounds, that the beneficial effects so far as glucosuria and hyperglycemia are concerned may disappear after five or six months on the oral hypoglycemic drug. This raises new questions: Are these patients becoming drug fast? More careless about their diets? Or are they obtaining poor control because they have been misled into believing that their diabetes was "cured" or needed less attention?

The risk to the lean diabetic patients subject to keto-acidosis on discontinuing insulin is so great that it seems mandatory to us that such patients be hospitalized for closer observation during trials of the drug.

Should the hypoglycemic agents be given to the overweight patient with mild or moderately severe diabetes? Why? Are we not obliged to recommend reduction of caloric intake for each of these subjects anyway? Are these compounds, like insulin, likely to lead to increased ingestion of food? That they cause hypoglycemia is not in question, even though this effect is inconstant. Even if they prove to have anabolic effects, do not weight reduction and calorie adjustment come first? At the moment it seems as if they are most effective where we do not need them, namely in the adult who is overweight and mildly diabetic. The sick, acidotic diabetic patient still needs insulin.

It is deplorable that information has been disseminated to create the false hope that diabetes is now an easily controlled disease because "tablets" are available. Our sickest diabetics are in no way helped by these compounds. And only some (albeit a majority) of mild diabetic patients are "helped" at all. It is deplorable that some announcements of benefit have been based on short preliminary observations without details of study or the use of suitable controls. It is to be hoped that all investigators of clinical diabetes will ponder the need for rigid selection of subjects under equally rigid supervision before administering the drug haphazardly.

The pharmaceutical companies concerned with the development of these compounds will as a matter of enlightened self-interest and public concern discourage the administration of the drugs to patients who do not need them or who, as in the case of the obese, may be defeated in attaining their goal of better health, lower weight and more normal metabolic balance. These companies have so far done a commendable job in the research and testing which is continuing in a cooperative manner with the investigators in the field of diabetes.

The development and marketing of insulin was achieved with the welfare of the diabetic patient carefully guarded by the clinical investigators and the manufacturers. The education of the physician and the patient towards effective management of diabetes is the finest form of regulation that medicine has offered for any disease. It is not yet in the interest of good medicine and the well-being of diabetic patients to support the release for marketing of an "insulin substitute" before adequate clinical testing and appraisal have been completed.

John Brisbane, M.D.

Irving Graef, M.D., New York City

The man pictured on the cover of this issue of the Journal is relatively unknown to students of the history of medicine and of diabetes in particular. He deserves better and wider appreciation on several counts.

John Brisbane, a Scotsman, lived in the eighteenth century; neither the date of his birth nor that of his death is presently recorded in the usual source books of biography. His death, however, is believed to have occurred about 1776.

Brisbane was a physician, a graduate of the University of Edinburgh in 1750 (D.M.I. de iis quae Medico ad artem bene exercendam adesse debent) and a member of the Royal College of Physicians from 1766. He held the post of physician to the Middlesex Hospital from 1758 until 1773 when he was superseded. According to a note in Munk's biographical work:[1] "In February, 1772, he obtained leave of absence from the hospital for three months — this in April was extended to a further period of six months, and in November to the 1st June, 1773. Failing then to return, the office of physician was declared vacant."

Two extremely interesting books reveal Brisbane to have been a man of great acumen, independence of thought and erudition, with ability as a painter and with the capacity for felicitous literary expression that has characterized so many physician-writers from Great Britain.

The two volumes published by him were *Select Cases in the Practice of Medicine,* 8 Vols., 1772 (G. Scott, London) and *Anatomy of Painting, with an Introduction giving a short View of Picturesque Anatomy,* fol. 1769. The latter work contains the six Tables of Albinus, the Anatomy of Celsus, with notes, and the Physiology of Cicero.

Choulant,[2] who has written a work on the history of anatomic illustration, gives another view of Brisbane that also illuminates his scholarship, creative power and culture:

"John Brisbane, doctor of medicine, was dissatisfied with the way in which anatomy was taught, and asked particularly for a short elegant manual of anatomy, with good drawings, for the use of the graphic or plastic artist and for the general information of the layman. He himself never dared to attempt such a book, but suggested that a scholarly anatomist, a man of good judgment and a highly cultivated mind undertake this task. He sets up as models: Celsus De medicina iv. I; Vii. 7, 18; viii. I, and the description of the human organization by Cicero in his de natura deorum, Lib. ii. He maintains that the artist has to study anatomy differently from the physician and the surgeon, namely from the point of view of his own art: 'for tho' physicians and surgeons have, for a long time, in a manner engrossed the whole business of teaching anatomy, yet painters, statuaries and engravers, should assert their rights, and teach and write upon this science in

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I am indebted to Dr. Arthur R. Colwell, Sr., for the biographical references and access to Brisbane's book, *Select Cases in the Practice of Medicine.*

a picturesque manner, suited to their own art,' et. He also thinks that more than is commonly believed can be accomplished by means of good illustrations, indeed he even holds that good illustrations may often serve the purposes of the artist better than personal dissection. He also presents Albinus' plates on a smaller scale as models, and, translating Albinus' own words, he describes Albinus' method of procedure. Out of these attempts grew the very rare, somewhat curious, but clever and highly instructive work under the following title:

"*The anatomy of painting, or a short and easy introduction to anatomy; being a new edition, on a smaller scale, of six tables of Albinus, with their linear figures; also, a new translation of Albinus's history of that work, and of his index to the six tables; to which are added the anatomy of Celsus, with notes, and the physiology of Cicero; with an introduction, giving a short view of picturesque anatomy.* (London, printed by George Scott, and sold by T. Cadell, 1769, fol.; 22 and 76 pp. and 12 copperplates in folio.)

"The plates represent three skeletons and three musclemen done on a small scale after Albinus and are all accompanied by outline-plates, on which special parts are repeated on a large scale in subordinate figures. The outline-plates are marked with engraved letters for explanation. The plates are praiseworthy, both from an artistic and an anatomic point of view. Each finished print is signed, at the bottom to the left: J. Brisbane M.D. delin. direxit editit. On the first plate, in the lower right-hand corner, P. Benazech is named as engraver. . . . For the other plates J. Caldwell is given as the engraver (James Caldwell, b. 1739). The text contains a preface and an introduction, an English translation of Albinus' preface to his Tabulae sceleti et musculor., an explanation of the plates, and lastly, under a separate title, the translations of the above-mentioned passages from Celsus and Cicero. A commentary is added to the former."

The clinical work is especially interesting to students of diabetes. In his book Brisbane wrote: "I have been near fourteen years physician to the Middlesex Hospital, and have spent above thirty years* in the study and practice of medicine. . . ." As to diabetes he said, "The true diabetes, as described by Aretaeus is a very rare disease . . . for Galen affirms that he saw this disease only twice; and Astruc in the populous city of Paris, never saw it at all. I have seen four cases of this disease, two of which came very near the description of Aretaeus, which for that reason I have translated into English, and subjoined."

Published with this biographical note (see pages 198-202) are reproduced pages of this remarkably captivating translation, including the statement of the circumstances under which Brisbane undertook the translation and of his own deep appreciation of the beauty of the early Greek writings.

In his book Brisbane comments on his patients in an equally engaging manner. Herewith are reprinted those pages which will be of interest to readers; note especially his concern with therapy: ". . . having then discovered the use of the tincture of cantharides, which in one case, I found so efficacious as even to cure; and in the other two was of great service."

It is interesting that Brisbane's book begins with his observations on the four cases of diabetes, the only ones he had seen.

Physicians interested in the evaluation of modern therapeutic agents may reflect with some concern the ever-recurrent tendency to attribute benefit to a particular therapeutic agent when waning of symptoms ensues. Note in Brisbane's fourth case that he recognized the role of psychological factors on the course of the patient's symptoms and how her diabetes "yielded remarkably to the tincture of cantharides, *along with the remedies usually given in hysterical complaints*" (italics mine).

John Brisbane must have been fascinated by diabetes as many have been since. His interest in Aretaeus' description and in translating it reflects a deep concern with the disorder.

*I cannot reconcile this estimate in a book published in 1772 and the stated year of graduation, 1750. Perhaps his medical studies began much earlier and were interrupted.

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SELECT CASES

IN THE

PRACTICE of MEDICINE.

By JOHN BRISBANE, M. D.

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Ὠφελιὴ δ' μὴ βλάπτειν.

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M.DCC.LXXII.

SELECT CASES

IN THE

PRACTICE of MEDICINE.

PART I.

SECT. I.

THE true diabetes, as deſcribed by Aretæus, is a very rare diſeaſe, and in ſome ages and nations it ſeems to have been rarer than in others; for

B Galen

up his body. Daily riding, conſerve of roſes, with aſs's milk, and other mild remedies, were the only things that did any good; and ſo long as he continued in the uſe of theſe, he ſpun out his time with tolerable eaſe. The diabetes I look upon to be, in many things, a-kin to a conſumption, the diſcharge by urine correſponding to the colliquative ſweats; and I treated it, in this gentleman, under that idea, not having then diſcovered the uſe of the tincture of cantharides, which, in one caſe, I found ſo efficacious as even to cure; and in other two it was of great ſervice. The above gentleman was

at

at laſt tired of his diſeaſe, and the mild remedies; and deſiring a conſultation of phyſicians older than me, they adviſed him to the uſe of the bark, which he continued for ſome time; but this medicine had no effect to relieve any one ſymptom; but on the contrary, loaded his ſtomach, palled his appetite, increaſed his thirſt, the dryneſs of his mouth, and the other ſymptoms; and in a word, brought him to his grave ſomewhat ſooner than he would otherwiſe have gone.

The ſecond caſe that occurred to me of the diabetes, was that

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Galen affirms, that he ſaw the diſeaſe only twice; and Aſtruc, in the populous city of Paris, never ſaw it at all. I have ſeen four caſes of this diſeaſe; two of which came very near the deſcription of Aretæus, which for that reaſon I have tranſlated into Engliſh, and ſubjoined. The third was more imperfect, and complicated with other diſorders. The fourth ſeemed to me to be of a ſpurious kind, though it was attended with ſome of the chief ſymptoms of the diabetes.

The firſt caſe I met with was in the year 1750, immediately after obtaining my degree as Doc-

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Doctor of Medicine. A gentleman of rank and fortune, a relation of my own, whoſe elder brother had died of the ſame diſeaſe, was ſeiſed with a diabetes. He had been many years valetudinary, and was pretty much advanced in years: he had moſt of the ſymptoms mentioned in the deſcription of Aretæus. I found almond emulſion, freely uſed as common drink, of very great uſe; as it not only nouriſhed him, and allayed his thirſt, but gave great relief to his hectic heats, and the burning at the ſcrobiculum cordis. Alum and other reſtringents had no effect upon his diſeaſe, but only bound up

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of William Weſtly, an out-patient at the Middleſex Hoſpital, a tall young coachman. The diſeaſe had been ſeveral months upon him before he paid much regard to it; but at length it attacked him with ſuch violence, that from a luſty ſtout young man, he was waſted to a ſhadow, and became ſo weak that he could hardly walk to the hoſpital, tho' very near his lodgings: on which account, I frequently viſited him there. Almond emulſion, with gum-arabic, I found of great uſe to him, as ſimple emulſion had been to the former patient; but alum and the bark were of no uſe; on the contrary, theſe and all

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all aſtringents were hurtful, and affected only the ſtomach and inteſtines, by binding the body: at laſt, his ſtrength being intirely waſted, ſo that he could hardly walk from his bed to a chair, and all his bad ſymptoms encreaſing, I gave him up for loſt; but endeavouring to form a theory of this uncommon diſeaſe, it came into my mind that it might, in ſome caſes at leaſt, be owing to a paralyſis, or other ſuch affection, of the nerves of the urinary paſſages: and knowing that cantharides had peculiar effects upon theſe parts, both in health and diſeaſes, I preſcribed ten gutts of the tincture of cantharides

tharides to be taken twice a-day in a wine-glaſs of water. Before he had taken this medicine four days, he found a change to the better; therefore I gradually increaſed the doſe to twenty, and afterwards to thirty gutts, making him continue the emulſion with gum-arabic, in order to prevent the irritation of the cantharides. By this method, his ſtrength and fleſh returned in a ſurpriſing manner: the quantity of his urine was greatly diminiſhed, and came near to the natural colour and taſte; for at firſt it was not only void of the ſalt or urinous taſte, but very mild and ſoft, and to me and ſome others

others appeared of a taſte ſomewhat ſaccharine or milky. Tho' this medicine occurred to me entirely from theory or ſpeculation, and from the general effects of cantharides on other occaſions, yet I afterwards found it had been uſed with ſucceſs by phyſicians in the diabetes, and was mentioned in one or two authors as uſeful in that diſeaſe.

The third caſe of the diabetes was that of another coachman, who came to me on hearing of the cure of the former patient: he was an older man, of a broken conſtitution, and ſubject to the gravel. By the uſe of the tinc-

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APPENDIX.

BEING in the country a few years ago, on account of my health, I amuſed myſelf with tranſlating the works of Aretæus, and ſome parts of Hippocrates, into Engliſh. The noble candour and ſimplicity of theſe antient authors, muſt delight every perſon of true taſte and judgment; though perhaps that very ſimplicity may appear inſipid, to thoſe whoſe taſte is formed on modern writers alone. The following is a faithful tranſ-

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lation of Aretæus's chapter on the diabetes; but it is not eaſy, along with the ſimplicity, to imitate the other beauties of the author, or the muſic and richneſs of the Ionic dialect.

Of the DIABETES.

"The diſeaſe of the diabetes is wonderful, and not common among men: it is a melting down of the fleſh and members into urine; the cauſe is moiſt and cold, as in dropſies, and by the uſual paſſage, the kidnies and bladder: the patient is perpetually making water, and the drain is inceſſant, like that from

open

ture of cantharides, he for ſome time found himſelf much better; but being obliged, on account of his other complaints, to proceed more ſlowly, and at the ſame time to take other medicines, he became impatient; and hearing of great cures performed by the waters at Briſtol, he went thither, and I have not heard of him ſince.

The fourth and laſt caſe of the diabetes, was that of a gentlewoman, about forty years of age: ſhe for ſome months had made great quantities of limpid water, almoſt without taſte or ſmell, attended with conſtant drought; but

but as her fleſh did not diminiſh, and as ſhe was affected with lowneſs of ſpirits, and other nervous ſymptoms, I conſidered her caſe to be partly nervous or hyſterical; and therefore that the diabetes might be ſaid to be ſymptomatic, or of a ſpurious kind. However, it yielded remarkably to the tincture of cantharides, along with the remedies uſually given in hyſterical complaints.

open canals. The nature of the diſeaſe is chronical, and is a long time in forming; and if it comes to its height, the perſon does not long ſurvive; for the waſting is rapid, and death comes quick, after a life moſt diſagreeable and painful; an unquenchable thirſt and much drinking, yet not equal to the great quantity of urine, and you can neither prevent them from drinking nor from making water; for if they refrain in the leaſt from drinking, the mouth becomes dry, and the bowels are, as it were, on fire: they are uneaſy and reſtleſs, and ſoon die with a burning thirſt: no method can pre-

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vent this drain of water, and the force of the diſeaſe overcomes modeſty; and if they but for a little ſtruggle againſt it, they ſwell in the loins, the hips and the teſticles; and when they remit their efforts, the urine again runs off plentifully, and the ſwelled parts ſubſide, diſcharging their load by the bladder.

When the diſeaſe is far advanced, it is eaſily known; but even before that time, the mouth is dry, the ſpittle white and frothy, as from thirſt, even before the thirſt comes on, a weight is felt about the hypochon-

chondria, and a ſenſe of heat, or of cold, paſſing from the belly to the bladder, pointing out, as it were, the road of the diſeaſe. At this time the urine begins to increaſe a little, and they have thirſt, but not very great.

But if the diſeaſe wax ſtronger, there is a ſmall but pungent heat fixed in the bowels, the abdomen is wrinkly, with large veins, and the whole body is emaciated, and then the urine and the thirſt increaſe greatly, and when a ſenſation comes to the end of the yard, they directly make water; and I imagine the diſeaſe is called diabetes, i. e. a

a paſſage or conduit, becauſe the water does not remain in the body, but the man becomes, as it were, a pipe or outlet to diſcharge it. The patient ſtill holds out a certain time, but not very long, becauſe he makes water to great exceſs, and a dreadful waſting enſues; for very little of the drink remains in the habit, and almoſt the whole fleſh is melted down into urine.

"The cauſe of the diabetes may be either acute diſeaſes diſcharging themſelves on theſe parts, and ſecretly leaving in their criſis ſome bad matter there, or elſe ſome poiſon that hurts

hurts the kidnies and bladder. Thus if one is bit by the dipſas, the ſymptoms reſemble the diabetes. The dipſas is a reptile which, by its bite, raiſes an unquenchable thirſt; and though drink is taken immoderately, the thirſt is not cured, but the belly is filled with redundant water; and if any, by reaſon of pain and diſtreſs from the diſtenſion of the belly, for a ſhort time refrain from drinking, thirſt obliges them ſoon to drink largely again; ſuch is the alternate attack of theſe evils, thirſt and drinking by turns diſtreſſing nature. Others have no diſcharge by urine; and there being

being no other vent, by exceſſive drinking, redundancy of water, and ſtretching of the belly, they ſuddenly burſt.

FINIS.

CORRESPONDENCE

To the Editor:

In a recent paper in this Journal, "Serum Lipids and Polysaccharides in Diabetes Mellitus" (*Diabetes* 5:116-20, 1956), Dr. David Adlersberg and his co-workers stated that "only scant information is available concerning complete serum lipid partitions" in diabetics with and without vascular complications, and in fact they quoted only one article from the literature (namely, J. Pomeranze and H. G. Kunkel: *Proc. Amer. Diab. Ass.* 10:217-31, 1950. From their results obtained in thirty-eight cases of uncomplicated diabetes and in twelve diabetics with retinopathy in whom they measured serum cholesterol, phospholipids and total lipids, the same authors drew the conclusion that diabetic patients with early retinopathy differ from uncomplicated diabetes by significant elevations of serum neutral fats and total lipids without any associated change in serum cholesterol and phospholipids."

I would like to point out that three years ago, while working at the Department of Metabolic Research, Wenner-Gren's Institute, Stockholm Högskola, I measured total lipids, cholesterol, lipid phosphorus and cholesterol-lipid phosphorus ratio in forty-one diabetics with retinopathy and fifty-nine diabetics without retinopathy (Iannaccone, A., and Kornerup, T.: Plasma lipids and diabetic retinopathy. *Acta. Med. Scand.* 148:411-16, 1954). Our conclusions were that plasma cholesterol and lipid phosphorus levels and the cholesterol-lipid phosphorus ratio were statistically equal in both groups, while the total lipids were significantly higher in diabetics with retinopathy.

I am glad that Dr. Adlersberg and co-workers confirm our previous results. Our American colleagues should not neglect European literature especially when it appears in the English language. I believe that the recent article of Dr. Joslin in this Journal (*Diabetes* 5:328-29, 1956) deserves much commendation in this respect.

ANGELO IANNACCONE, M.D.
Assistant Professor of Internal Medicine
University of Florence, Italy
Member of the American Diabetes Association
Jan. 3, 1957

To the Editor:

We are familiar with the interesting publication of Doctors A. Iannaccone and T. Kornerup. However, this article was not known to us at the time our study was being conducted and prepared for publication (1953 and 1954). Our paper was read before the Annual Meeting of the American Diabetes Association in June of 1955, and it was published approximately one year later in DIABETES. The processing of scientific publications is very slow at times in our country and perhaps in other countries, as well. To illustrate the difficulty in keeping up with the medical literature, we would like to point out that Dr. Iannaccone and his colleague omitted to quote an American study on serum lipids in diabetes mellitus published in 1950, namely the paper by Pomeranze and Kunkel.

The study of Doctors Iannaccone and Kornerup and our own study had completely different objectives. Doctors Iannaccone and Kornerup studied serum lipids in diabetic patients with and without retinopathy. Our study was concerned with a simultaneous correlative analysis of serum lipids and polysaccharides in normal controls (Group I), in patients with uncomplicated diabetes (Group II), in especially selected patients with early diabetic retinopathy and no evidences of hypertensive retinopathy, proteinuria or manifest renal involvement (Group III), and finally in a group of patients whose severe retinopathy was associated with hypertension, edema and proteinuria and of whom many had evidences of renal insufficiency (Group IV).

The most striking elevation of all serum lipid fractions as well as of serum polysaccharides was found in Group IV. It was of particular interest, however, that patients in Group III with early retinopathy without any evidence of renal involvement presented increases in serum triglycerides, total lipids, serum glucosamine and total serum polysaccharides in the presence of normal serum cholesterol and phospholipid levels.

A strict comparison of the results of the two papers even in relation to serum lipids is impossible, since patients with diabetes studied by Doctors Iannaccone and Kornerup were divided into two groups only on the basis of the presence or absence of retinopathy without special reference to other complications. We are happy, nevertheless, that somewhat similar observations in regard to serum lipids were made independently by Doctors Iannaccone and Kornerup in Stockholm and by our two groups in New York.

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The Mount Sinai Hospital, New York
HAROLD RIFKIN, M.D.
Montefiore Hospital, New York
April 2, 1957

BOOK REVIEWS

THE INQUISITIVE PHYSICIAN—THE LIFE AND TIMES OF GEORGE RICHARDS MINOT, M.D. *By Francis M. Rackemann, M.D. $5.00, pp. 288, Harvard University Press, Cambridge, Massachusetts, April 1956.*

That Dr. George R. Minot had diabetes for twenty-nine years is less well known than the fact that he discovered the cure for pernicious anemia and received the Nobel Prize for his achievement. It was in 1921 that he developed severe diabetes and it was dramatic indeed that the discovery of insulin saved him from almost certain death. From the very day of onset the care of his diabetes was under the direction of Dr. Elliott P. Joslin.

In 1926 Minot's famous paper was read at the Annual Meeting of the Association of American Physicians. It was entitled "Observations on Patients with Pernicious Anemia Partaking of a Special Diet," and was divided into two parts: a. Clinical aspects by George R. Minot and William P. Murphy; and b. Physiological aspects by William P. Murphy, Reginald Fitz and Robert D. Monroe. In this famous paper the results of the use of liver in the treatment of pernicious anemia were announced. It was followed by the isolation of liver extract; the modern treatment and control of pernicious anemia was then established.

This charmingly written biography provides such scrupulous documentation that the reader is made to participate in the achievements and friendships not only of Dr. Minot but of a distinguished group of American physicians during the last forty years. The medical profession surely owes a debt of gratitude to Dr. Rackemann.

Dr. Minot was born in 1885; his ancestors had lived in America since 1630. From them came his inquisitive spirit and his industry; but more important was a background of culture that gave him integrity. As a boy he was interested in natural history, and thought often of becoming a doctor, but his poor general health made him hesitate. Finally, however, he entered Harvard Medical School, even though it appears to have been almost by chance. His interest in medical science then became consuming. Dr. Rackemann, his cousin, classmate in medical school and warm friend throughout his life, presents in this biography a description of his student days, his years as intern at the Massachusetts General Hospital and then as assistant to Dr. William S. Thayer at Johns Hopkins Hospital in Baltimore. His work in the laboratory of Professor Howell led to his interest in the study of the blood. Upon his return to the Massachusetts General Hospital and then at the Huntington Hospital his investigations resulted in many publications in hematology.

During all these years the friendship with Dr. Francis Peabody, four years his senior, had meant so much to him. When Dr. Peabody died on Oct. 13, 1927, the loss was very direct and personal. Gone was a young man in the prime of life. His death was a serious loss to both the Harvard Medical School and Thorndike Memorial Laboratory at the Boston City Hospital. The choice of Dr. Minot by the Harvard Medical School as Director of the Thorndike Memorial Laboratory was most fortunate and yet in no place in this book is there more striking evidence of the humility of Dr. Minot than in the letter which is quoted by Dr. Rackemann, "How can I ever come within miles of serving American medicine and our school as Francis did? I do not know."

Dr. Minot's years at the Thorndike Memorial Laboratory were marked by the selection of able assistants. Among the four hundred men who received training at the Thorndike, many have become physicians of high responsibility in medical teaching and investigation. During this period his own research activities diminished as his time was given more and more to the stimulation of the group of investigators in the laboratory.

Many honors came to Dr. Minot. They included an honorary degree of Sc.D. from Harvard University and the award of the Distinguished Service Medal by the American Medical Association. In 1934 he was awarded the Nobel Prize in Medicine, and the story about his trip to Sweden makes interesting reading.

The author has made a warm appraisal of his personal qualities and has included the remarks of his many friends. Dr. Minot had a curiosity and avidity for understanding that drove his mind into new regions for investigation. A capacity for details made him an excellent teacher in the ward. Here he pressed inquiries into the patients' habits of living and working which emphasized to his students his genuine concern for the patient as a person. He once ended a presidential address with this sentence, "To teach the art of courageous living is often the chief prescription for the patient with chronic arthritis." Dr. Rackemann concludes that if ever a man practiced the art of courageous living it was George Richards Minot.

ABSTRACTS

Allegretti, Niksa; Est, Mladen; and Uraic, Durda (Dept. of Physiol., Univ. of Zagreb, and Ruder Boskovic Inst., Zagreb, Yugoslavia): ALLOXAN ADMINISTRATION IN THE GUINEA PIG WITH ACINOUS TISSUE ATROPHIC RENDERED BY LIGATURE OF THE PANCREATIC DUCT. Endocrinology 59:131-34, July 1956.

Evidence is presented suggesting that guinea pig islets can regenerate or develop from acinous tissue. Work is reported in which guinea pigs had the main pancreatic duct ligated, were given a diabetic dose of alloxan six weeks later, and then demonstrated atrophy of acinous tissue and showed no evidence of diabetes.

Annotation: INSULIN-NEUTRALIZING ANTIBODIES. Lancet 2:452, Sept 1, 1956.

The author comments on the problem of insulin resistance and the various technics which have been developed to detect and measure insulin-neutralizing antibodies. These include the protection of mice and rabbits from insulin-induced hypoglycemia, precipitin tests (or measurements of the precipitin by the agglutination of collodion particles coated with insulin in the presence of antiserum) and hemagglutination methods or glycogen uptake studies on the rat diaphragm. The anti-insulin activity resides in certain specific gamma globulins. Successful treatment, aimed at depression of excess globulin formation in patients with insulin resistance, has been reported in which ACTH or cortisone was used.

Bastenie, Paul (Clinique Méd. Hôpital Universitaire St.-Pierre, Brussels, Belgium): SOME EFFECTS OF BZ-55 ON THE CARBOHYDRATE METABOLISM OF DIABETIC PATIENTS. Lancet 2:628, Sept. 22, 1956.

The author reports on twelve diabetic patients who did not require insulin treatment and who were given BZ-55 followed by various laboratory function tests. All showed the same reduction of blood glucose and glycosuria that has been described previously by other authors. In only four of the twelve, however, was there any improvement of the glucose-assimilation coefficient. There was no constant change in the action of exogenous insulin, as judged by various function tests. This observation seems to rule out a true insulin-sparing action of the sulfonamide. The only definite change observed in all the patients was the very marked depression (in most cases the disappearance) of the output of glucose by the liver during the insulin-induced hypoglycemia. This observation is in keeping with recent reports suggesting that the sulfonamides producing hypoglycemia inhibit important enzyme systems (among them glucose-6-phosphatase) in the liver. The reduction of glucose output by the liver and the reutilization of glucose might explain why the blood of diabetics treated with BZ-55 or related compounds contains an excess of pyruvate and also the reason for the lowering of blood glucose and the increase in body weight.

Bauer, Julius (Los Angeles, Calif.): INSULIN-NEUTRALIZING ANTIBODIES. Lancet 2:732, Oct. 6, 1956.

The author replies to an annotation in this journal (Sept. 1, 1956) which made reference to his previous investigative work on antibody formation against insulin. The appearance of these antibodies, produced experimentally in rabbits, was not associated with a higher resistance of the animals against insulin. Three patients with spontaneous hypoglycemia, one of whom had a proved insuloma of the pancreas, also gave a positive complement fixation with insulin as antigen.

Beaser, Samuel B. (Diabetic Clin. of Med. Serv., Beth Israel Hosp., Harvard Med. Sch., Cambridge, Mass.): MEDICAL PROGRESS: DIABETES MELLITUS. New England J. Med. 255:173-79, July 26, 1956; 223-31, Aug. 2, 1956.

This is an excellent review of some of the newer developments in the field of diabetes. The material covered includes carbohydrate metabolism, fat and protein metabolism, insulin and its metabolism, endocrine effects of carbohydrate metabolism, pathology and pathogenesis, diagnosis, clinical diabetes, therapy, pregnancy and diabetes, and complications, acute and degenerative.

Brand, William (London, England): EXACT CONTROL IN DIABETES (NOTES AND COMMENTS). Brit. M. J. 2:836, Oct. 6, 1956.

The author inquires as to the importance of strict control in the management of diabetes mellitus and questions the harmful effects of long-term hyperglycemia and glycosuria. The reply to his query cites detailed follow-up studies of large numbers of cases which seem to indicate the harmful effects of poor diabetic control with relation to the incidence of degenerative changes.

Campbell, James; and Best, Charles H. (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): PHYSIOLOGIC ASPECTS OF KETOSIS. Metabolism 5:95-113, March 1956.

Acetoacetate is the first ketone produced in the body and is the source of 1-*b*-hydroxybutyrate, which appears in body fluids during diabetic acidosis. It is assumed that acetone results from a spontaneous, nonenzymatic decarboxylation of acetoacetate in the body and in the urine. Though the fatty acids are the chief precursors of ketones, the amino acids leucine, tyrosine and phenylalanine may be changed to ketone bodies in the tissues. Under special circumstances, pyruvate may be converted acetoacetate.

Although the liver is the main source of ketone production, acetoacetate may be formed in other tissues, e.g., kidney. Extrahepatic tissues readily utilize acetoacetate and *b*-hydroxybutyrate at a rate related to their concentration. Their utilization by muscle appears to be independent of the influence of insulin. Furthermore, there has been failure to demonstrate that carbohydrates influence ketone utilization experimentally in eviscerate animals. It seems now that ketones appearing after pancreatectomy are the result of overproduction of ketones by the liver.

Ketone bodies, normally occurring during fatty acid oxidation, may well constitute a source of energy. Overproduction is abnormal and often injurious, since it upsets acid-base balance with loss of base from body fluids. Ketone body production is probably controlled by the ability of liver cells to utilize available carbohydrate.

Acetyl CoA is the active acetate involved in the oxidation and synthesis of fatty acids. From this acetoacetyl is formed. The extrahepatic tissues may reduce acetoacetyl to *b*-hydroxybutyrate, with oxidation to CO_2 and H_2O. The liver may use CoA for a number of enzymatic reactions, particularly in relation to the Krebs cycle.

Diabetes resulting from pancreatectomy results in loss of carbohydrate, protein and fat reserves, and the liver shows an increase in fat deposition. Whereas insulin corrects these disorders, hypophysectomy only reduces them while preventing deposition of fat in the liver of such animals. However, liver-tissue technics reveal that normal hepatic lipogenesis requires at least some, if not all, of the hormones produced by the pituitary gland. These hormones, acting in a manner opposite to insulin, increase the utilization of fat in the body and cause accumulation of lipid, increased production of acetoacetate and decreased formation of fatty acids in the liver.

Carne, Stuart (London, N.W. 2, England): ENZYME TESTS FOR GLYCOSURIA. Brit. M. J. 2:827-28, Oct. 6, 1956.

The author reports the results of his testing of the urine of diabetic patients with the newer enzyme tests and comments on the precautions that must be taken to evaluate the results properly.

Chambers, R. A.; and Pratt, R. T. C. (National Hosp., Queen Square, London, and Maida Vale Hosp., London, England): IDIOSYNCRASY TO FRUCTOSE. Lancet 2:340, Aug. 18, 1956.

The authors report a patient with an idiosyncrasy to fructose, which was manifested by vomiting after its ingestion. This condition differs from benign fructosuria, in which the excretion of a proportion of ingested fructose is not accompanied by the symptoms of intolerance displayed by this patient, presumably caused by the accumulation of a toxic intermediate. The practical importance of this observation is that idiosyncrasy to fructose should be considered as one cause of difficulty in weaning.

Conn, Jerome W.; and Fajans, Stefan S. (Div. of Endocrinol. and Metab., Dept. of Int. Med., Univ. of Michigan Med. Sch., Ann Arbor, Mich.): INFLUENCE OF ADRENAL CORTICAL STEROIDS ON CARBOHYDRATE METABOLISM IN MAN. Metabolism 5:114-27, March 1956.

The effects of the glucocorticoids in diabetics and nondiabetics are reviewed. It is pointed out that, in adrenal insufficiency, physiological amounts of hydrocortisone will prevent fasting hypoglycemia, decrease exogenous insulin sensitivity, increase urinary nitrogen during fasting and produce a fall in the previously high fasting respiratory quotient.

Hydrocortisone and compound B increase gluconeogenesis from protein and inhibit peripheral utilization of glucose.

Excessive secretion of hydrocortisone, as seen in Cushing's syndrome, results in a loss of carbohydrate tolerance that is usually reversible on surgical removal of the adrenal lesion. In addition, the blood lactate and pyruvate levels may be greatly elevated.

It is well recognized that the administration of ACTH, hydrocortisone and cortisone may produce decreased glucose tolerance, fasting hyperglycemia and glycosuria. The degree of disturbance varies more or less directly with the amount given and the duration of administration. The diabetic state is nearly always reversible on discontinuance of the hormone. The glycosuria that appears may be due to a decrease in renal tubular reabsorption for glucose or may be the result of hyperglycemia. The latter is due to increased gluconeogenesis

and impaired utilization of glucose.

The comparative potency of the natural steroids upon carbohydrate metabolism finds hydrocortisone the most potent, then cortisone, followed by compound B and compound A.

Although ACTH and cortisone intensify the diabetic state, they are not contraindicated from a clinical point of view in diabetes. They produce a diabetic state in relatives of diabetics more commonly than in individuals without a family history of diabetes. Future studies of the application of this principle may reveal a means for predicting future diabetes.

There are, at the present time, studies indicating that patients with diabetes mellitus have decreased adrenal cortical function. On the other hand, Becker and his colleagues report evidence that patients with diabetic retinopathy have increased adrenal cortical function.

ACTH and hydrocortisone are useful in the treatment of idiopathic spontaneous hypoglycemia in infants and young children and in the treatment of hypoglycemia due to anterior pituitary insufficiency and adrenal cortical insufficiency.

Constam, G. R.; Bonhôte, D.; Fellmann, H.; Heller, A.; Labhart, A.; Spühler, O.; and Wenger, V. (Med. Policlinic, Univ. of Zurich and City Hospital, Zurich, Switzerland): ON BLOODSUGAR LOWERING SULFONAMIDES. Schweiz. med. Wchnschr. 86:699-705, June 16, 1956.

In trying to elucidate the mode of action of N_1-sulfanilyl-N_2-n-butylcarbamide (Nadisan), the authors made the following observations:

Blood sugar curves after intravenous injection of glucagon are not changed by Nadisan. Intravenous glucose tolerance tests in diabetics before and during Nadisan therapy show a higher rise followed by a more rapid fall of the blood sugar under the influence of this sulfonamide. The former may be due to the suppression of glycosuria; the latter, to increased homeostatic blood sugar regulation or to intensified insulin action. Lowering of the inorganic phosphate content in the blood speaks in favor of the last mentioned possibility.

Insulin tolerance tests in normal and in diabetic persons were not altered by Nadisan, which apparently does not influence the action of intravenously injected insulin. In Nadisan-resistant diabetics, the blood sugar curves kept their falling tendency throughout the two hours of the tests; whereas in Nadisan-sensitive patients, the blood sugar started to rise again 30 to 45 minutes after the injection of insulin.

Nadisan had no influence on the corticoid content of the plasma or on the steroid excretion in the urine. The action of ACTH on the suprarenal gland is not inhibited by Nadisan. The latter does not cancel the lowering of glucose tolerance by infusions of cortisol. Nadisan produced severe hypoglycemia in a case of panhypopituitarism. Evidently the blood sugar lowering action of Nadisan is not obtained by inhibition of the pituitary gland or the adrenal cortex. It seems more probable that Nadisan increases the efficiency of the endogenous insulin.

Summarizing their experience with their first 100 diabetics treated by Nadisan, the authors mention that they have not observed any serious side effects but that the time of observation is too short for final judgment. They believe that sulfonamides should not be used in diabetics who can be well controlled by diet alone or in infants or juvenile patients. Nadisan is quite efficient in overweight persons who are over forty-five years old and whose diabetes was discovered less than five years before. In underweight persons or in diabetics of longer standing, it is impossible to predict the action or nonaction of Nadisan. In some cases of insulin resistance, the new drug is valuable. For acute conditions like acidosis and during infections or operations, insulin is to be used. (German)

Cooper, David A.; and Marshall, E. Wayne (Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.): DIABETES AND TUBERCULOSIS. M. Clin. North America 39:1643-54, November 1955.

The susceptibility of patients with diabetes to pulmonary tuberculosis is again stressed; and clinical data from a survey of the Philadelphia area, together with other authors' reports, are presented. Proper control of the diabetic with tuberculosis is stressed as being extremely important in the treatment of this disease. Etiological factors in pulmonary tuberculosis in diabetics are discussed, and the diagnostic studies and treatment are presented. Preventive measures, in the form of frequent chest X-ray examinations of diabetic patients, are recommended; and the maintenance of adequate nutrition and vitamin intake, as well as avoidance of exposure to tuberculosis, is recommended for all diabetic patients.

Creutzfeldt, W. (Medizinschen Universitätsklinik in Freiburg, Germany): MORPHOLOGICAL CHANGES OF THE PANCREATIC ISLETS AND THEIR RELATIONSHIP TO CARBOHYDRATE METABOLISM; WITH SPECIAL REFERENCE TO PERORAL ANTIDIABETIC DRUGS. Wien. Zschr. inn. Med. 37:217-230, June 1956.

This is a thorough review of present knowledge about the relationship of islet-cell morphology to carbo-

hydrate metabolism. Although a fairly good relationship exists between histological changes in the beta cells on one hand and blood sugar changes on the other, there is as yet no clear correlation between the histology of the alpha cells and the blood sugar level. Certain hypoglycemic agents, as, for instance, synthalin B, cause alpha cell damage, but such damage may occur also without disturbance of the blood sugar homeostasis. Synthalin B is hepatotoxic. Alpha cell damage is seen not infrequently in association with liver damage, as, for instance, after carbon tetrachloride poisoning. Some of the hypoglycemic sulfonamides cause alpha cell damage; others do not. It seems therefore that such alphacytotoxic action is not essential for the hypoglycemic activity of these compounds. Experimental studies and clinical observations do not as yet support the concept that quantitative or qualitative changes in the alpha cells disturb the carbohydrate metabolism. Likewise it is still uncertain what physiological role is played by the hypoglycemic glycogenolytic factor, glucagon, which is thought to be formed in the alpha cells.

Duncan, Garfield G. (Jefferson Med. Coll., Pennsylvania Hosp. and Benjamin Franklin Clin., Philadelphia, Pa.): SOME ATTEMPTS TO SIMPLIFY THE TREATMENT FOR DIABETES AND ITS ACUTE COMPLICATIONS. M. Clin. North America *39*:1579-86, November 1955.

The author outlined simplified methods for the treatment of diabetes and its acute complications, including discussion on the detection of diabetes and the type of insulin therapy fitted to different types of diabetes, according to severity. Outlined treatment for diabetic coma is also presented.

Duncan, L. J. P. (Dept. of Therapeutics, Univ. of Edinburgh, Scotland): THE INTRAVENOUS GLUCOSE TOLERANCE TEST. Quart. J. Exper. Physiol. *41*:85-96, January 1956.

Two indices of glucose tolerance, the "total index" and the "increment index," derived from an intravenous glucose tolerance test, are defined, and values for them have been determined in twenty normal and fifteen diabetic subjects. Either index (K) is defined by the following equation:

$$K = \frac{\log_{10} C_1 - \log_{10} C_2}{t_2 - t_1} \times 2.3$$

C_1 and C_2 are the total blood glucose concentrations at times t_1 and t_2 respectively, for total index indices. C_1 and C_2 are the increases above the initial fasting blood glucose levels at times t_1 and t_2 respectively, for increment index indices.

The total index is based on the assumption that the rate of fall of blood glucose remains consistently proportional to the total blood glucose value. The increment index assumes that the rate remains proportional to the increment in blood glucose value.

The mean total index for forty-two tests in twenty normal subjects was 1.37, and the mean increment index was 3.68. The mean total index for twenty-one tests in fifteen mildly diabetic patients was 0.71, and the mean increment index was 1.83.

With a constant loading dose of glucose, both indices are reproducible in any one individual. Increasing the loading dose from 25 to 50 gm. produced significant increases of the total index in eight normal and six diabetic subjects. The increment index remained constant in both groups. The increment index is, therefore, the preferable measure of intravenous glucose tolerance.

Duncan, L. J. P.; Baird, Joyce D.; and Dunlop, D. M. (Edinburgh Univ., Edinburgh, Scotland): A CLINICAL TRIAL OF BZ-55. Brit. M. J. *2*:433-39, Aug. 25, 1956.

The authors state that BZ-55 proved to be an effective substitute for insulin in thirty-three of fifty-five middle-aged or elderly diabetic patients. The drug was without effect on ketosis or in patients who readily developed ketosis. The difficulties in selecting responsive patients and the dangers in withdrawing insulin in unresponsive patients are emphasized. The character of the hypoglycemic response obtained has been analyzed. Data from follow-up studies reveal that maintenance treatment with BZ-55 must be continuous and not intermittent. Minor toxic effects were encountered in several patients, and there appears to be a possibility that thrombocytopenia may occur with alarming frequency. BZ-55 is not a substitute for dietary restriction. If this principal is observed, the number of patients in whom it can replace insulin is more limited than reports to date have suggested.

Duncan, L. J. P.; Nabarro, J. D. N.; Oakley, W. G.; and Wolff, F. W. (Edinburgh Royal Infirmary, Scotland Middlesex Hosp., King's Coll. Hosp., Wellcome Research Institute, London, England): A WARNING NOTE. Brit. M. J. *2*:454, Aug. 25, 1956.

In view of a recent report from America of a small number of cases of severe agranulocytosis and also of several cases of thrombocytopenia in Great Britain, it is the considered opinion of the authors of the papers on BZ-55 appearing in the Aug. 25, 1956, issue of the *British Medical Journal* that the drug in question should at present be used only under careful hospital supervision. This view is shared by the majority of those

who have had experimental and clinical experience with the use of BZ-55 in Great Britain.

Editorial (London, England): GLUCAGON. Brit. M. J. *2*:288-89, Aug. 4, 1956.

The author reviews the present status of glucagon and concludes that there is good evidence that it is a second hormone of the pancreas. It is probably secreted by the alpha cells of the pancreatic islets and may be under the control of the growth hormone. Glucagon appears to be one of the factors concerned in the regulation of the level of blood sugar, both in health and in the diabetic state, but its role would seem to be no more than a subsidiary one.

Editorial (London, England): HYPOGLYCAEMIC SULPHONAMIDES. Brit. M. J. *2*:465-67, Aug. 25, 1956.

The author reviews the history and present status of hypoglycemic sulfonamides and comments on the unresolved controversy concerning their mode of action and their toxic effects.

Engleson, Gunnar; and Lehmann, Orla (Paediatric Dept., Univ. Hosp., Lund, Sweden): BZ-55 IN JUVENILE DIABETES. Lancet *2*:786, Oct. 13, 1956.

The author reports his experience with BZ-55 in diabetic children and believes that the new hypoglycemic sulfonamide preparations are of limited value.

Fagerberg, Sven-Erik (Med. Clin. I, Sahlgren's Hosp., Gothenburg, Sweden): STUDIES ON THE PATHOGENESIS OF DIABETIC NEUROPATHY: SURVEY OF THE LITERATURE AND OWN WORKING HYPOTHESIS. Acta med. scandinav. *154*:145-50, 1956.

A survey of the literature is given regarding the various opinions which have been stated about the pathogenesis of the diabetic neuropathy. The vascular theory has been studied more extensively. The research carried out during recent years has strongly supported the idea that the various vascular symptoms in long-standing diabetes manifest in different ways a generalized, specific vascular disease—diabetic angiopathy. By means of (*inter alia*) histopathological examinations of the sural nerve, the author has tried to show that diabetic neuropathy probably has the same pathogenesis as the retinopathy and the nephropathy.

Feinblatt, Theodore M.; and Ferguson, Edgar A., Jr. (Brooklyn, N. Y.): INSULIN ADDITIVES: GLUCAGON, NITROGENOUS SUBSTANCES, METALLIC ELEMENTS, AND SPECIFIC PHARMACODYNAMIC AGENTS. Southwestern Med. 37:298-99, May 1956; 370-73, June 1956; 422-24, 1956.

The authors discuss the effect of the above-named insulin additives on insulin and conclude that the additives could be arranged in three groups: those causing faster insulin effect, those causing normal effect and those causing delayed insulin effect.

Forster, H. Walter, Jr. (Woman's Med. Coll. of Pennsylvania; Episcopal Hosp., Philadelphia, Pa.): OCULAR DIABETES. M. Clin. North America *40*:1641-52, November 1956.

This article is an excellent summary of all of the permanent and transient changes that may occur in the eyes secondary to diabetes mellitus, and the treatment of these conditions is presented. The refractive error which occurs in diabetes because of elevated blood sugar and the pitfalls that ophthalmologists may get into by refracting in diabetes not under control are mentioned. The exact mechanism of the refractive error in hyperglycemia is not definitely known, but it is thought to be due to osmotic changes between the fluid of the lens and the aqueous fluid of the eye. The problem of diabetic cataracts, including juvenile diabetic cataracts, is discussed. Visual defects, such as field defects or central scotoma, may occur in the eye secondary to diabetic lesions of the visual pathways and brain stem.

The author presents an ophthalmic classification of diabetic retinopathy in four stages:

Stage I. Microaneurysms in the small venules and distention of the retinal veins.

Stage II. Includes Stage I, plus deep retinal punctate hemorrhages and waxy exudates.

Stage III. Includes Stage II, plus superficial retinal hemorrhages, dilatation of existing capillary networks, neovascularization, preretinal hemorrhages and fibrosis of the surface of the retina resulting from organization of retinal hemorrhages.

Stage IV. Includes Stage III, plus vitreous hemorrhages, proliferating retinopathy with its sequelae—rubeosis iridis, retinal detachment, secondary glaucoma, and loss of useful vision.

The therapy of diabetic retinopathy at the present time, according to the author, is not satisfactory. Several forms of treatment, including decreasing capillary fragility, use of ascorbic acid, steroid therapy, X-ray therapy and the experimental bilateral adrenalectomy and hypophysectomy, are discussed briefly. In summary, the author feels that there is no satisfactory prevention or treatment of diabetic retinopathy but that it is generally thought that the strict control of the diabetes is still the best preventive measure. The author does recommend the use of ascorbic acid, vitamin B_{12} in large doses, and testosterone combined with estrogen in the form of estradiol benzoate injection.

Ghanem, M. H.; and Mikhail, Maurice N. (Univ. of Alexandria, Egypt): RESPONSIVENESS TO ORAL HYPOGLYCAEMIC AGENT. Lancet *2*:514, Sept. 8, 1956.

The authors comment on a method of testing a diabetic patient's sensitivity to the hypoglycemic effect of BZ-55.

Ghanem, M. H.; and Mikhail, Maurice N. (Univ. of Alexandria, Egypt): RESPONSIVENESS TO ORAL HYPOGLYCAEMIC AGENT. Lancet *2*:898, Oct. 27, 1956.

The authors comment on studies they have utilized to predict responsiveness to hypoglycemic sulfonamide therapy in diabetics.

Gifford, Edward S., Jr. (Graduate Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.): THE UNSOLVED PROBLEM OF DIABETIC RETINOPATHY. M. Clin. North America *39*:1671-83, November 1955.

The earliest sign of diabetic changes in the retina is often the appearance of microaneurysms. The author discusses the appearance and development of further changes, in the form of hemorrhages and exudates, and compares them to the changes associated with arteriosclerosis and other pathological conditions of the retina. A brief discussion is also offered of Kimmelstiel-Wilson's disease and the similarity of the lesions of the kidney and the retinal lesions. The statement is made that those cases in which kidney lesions are found will almost always have associated retinopathy. The progressive nature of diabetic retinopathy in pregnancy is also discussed.

Several forms of treatment are set forth, including drug therapy with rutin and vitamin P, testosterone, vitamin B_{12} and steroid therapy, all of which apparently have shown rather poor results. X-ray therapy to the eyes is also discussed. The author felt that it should be used in the early stages of proliferating retinitis to be of benefit and that it would have very little value in the advanced cases. It was reiterated that rigid control of the diabetes was the most important factor in preventing and retarding the development of retinopathy.

Glicksman, Arvin S.; Myers, W. P. Laird; and Rawson, Rulon W. (Genl. Med. and Chemother. Serv., Dept. of Med., Memorial Hosp.; and Div. of Clin. Invest. and Clin. Chemother., Sloan-Kettering Inst., New York, N. Y.): DIABETES MELLITUS AND CARBOHYDRATE METABOLISM IN PATIENTS WITH CANCER. M. Clin. North America *40*:887-900, May 1956.

The authors give a quite detailed treatise on the problem of the association of altered carbohydrate metabolism and cancer. They review the literature on the occurrence of diabetes mellitus and cancer and also on abnormal glucose tolerance curves as related to cancer. In their own series of 850 consecutive cases studied, they found that impaired carbohydrate metabolism occurred in 34.5 per cent of the cancer population, as opposed to 9.9 per cent in a benign group.

A discussion theorizing the possible mechanisms involved and a consideration of the enzymology and hormonal environment of tumors is given.

There is also a detailed discussion of the problems of clinical diabetes in cancer, consisting in care of the diabetic through preoperative and postoperative management of cancer patients and the difficulties involved. Mention is also made of the problem of the use of adrenal steroids in treatment of malignancies and the possibilities of developing diabetes while under steroid therapy.

Havens, W. Paul, Jr. (Jefferson Med. Coll., Philadelphia, Pa.): VIRAL HEPATITIS AND DIABETES MELLITUS. M. Clin. North America *39*:1685-91, November 1955.

The author presents two cases of coexisting diabetes and viral hepatitis which illustrate the fact that patients with diabetes usually tend to have a more prolonged and serious course of the disease. The diabetic state is usually more severe throughout the course of the disease; and, after recovery, the diabetic condition often remains more severe in the future. A brief discussion of the etiology of hepatitis is offered, and the effect of hepatic disease on carbohydrate metabolism is discussed.

Hunt, J. A.; Gray, C. H.; and Thorogood, D. E. (Dept. of Diabetes, King's Coll. Hosp. & King's Coll. Hosp. Med. Schl., London, England): ENZYME TESTS FOR THE DETECTION OF GLUCOSE. Brit. M. J. *2*:586-88, Sept. 8, 1956.

The authors have made a comparison between two new enzyme tests for the detection of glucose and existing methods. Both tests are equally good in this respect. They are highly specific for glucose and may be of great value either to supplement existing tests or perhaps to take their place. The claim that one of these tests permits accurate estimation of glucose is not confirmed.

Hunt, J. A.; Oakley, Wilfrid; and Lawrence, R. D. (Diabetic Dept., King's Coll. Hosp., London, England): CLINICAL TRIAL OF THE NEW ORAL HYPOGLYCAEMIC AGENT BZ 55. Brit. M. J. *2*:445-48, Aug. 25, 1956.

The authors report on the use of BZ-55 in a total of thirty-eight diabetic patients. The presence of significant ketonuria, either in patients treated by diet alone or after the withdrawal of insulin, was constantly as-

sociated with complete failure to respond to BZ-55. In general, it appeared that young diabetics and those requiring more than small doses of insulin showed little or no response, nor was there reliable evidence that the administration of BZ-55 to such patients decreased their insulin requirements. No constant relationship could be demonstrated between the response to BZ-55 and the age of the patient, the duration of the diabetes, or the duration of insulin therapy. The factors in patients most constantly related to responsiveness to BZ-55 were the age of onset of diabetes (over forty years in all cases) and absence of more than minimal ketonuria while on dietary control without insulin. These results lend support to the findings of others who have carried out more extensive trials with BZ-55.

Ingle, Dwight J. (The Ben May Lab. for Cancer Res., Univ. of Chicago, Chicago, Ill.): URINARY GLUCOSE AND TUMOR GROWTH IN DIABETIC RATS. Endocrinology 59:259-60, August 1956.

Rats were made diabetic by partial pancreatectomy and forced feeding. Urinary glucose was determined and compared in a group of diabetic rats, a group of diabetic rats implanted with Walker Carcinoma 256, and a group of nondiabetic rats implanted with tumor. Growth of tumor was suppressed in diabetic rats, which also showed a decrease in glucose excreted.

Knox, Kenneth R. (Div. of Med., Pennsylvania Hosp., Philadelphia, Pa.): MANAGEMENT OF THE OVERWEIGHT DIABETIC PATIENT. M. Clin. North America 39:1599-1606, November 1955.

Most overweight diabetic patients can be treated by a reduction diet alone. The author stressed that the diet should provide fewer calories than the organism requires to support his over-all total body metabolism, sufficient protein to insure against utilization and depletion of endogenous protein, negative nitrogen balance, adequate fat for palatability and the required amounts of minerals and vitamins. The use of insulin is sometimes necessary in slightly overweight individuals. The psychogenic aspects of obesity are also discussed briefly.

König, M. P. (Med. Clin., Univ. of Berne, Switzerland): A SIMPLIFIED METHOD FOR URINE SUGAR DETERMINATION, TES-TAPE LILLY. Schweiz. med. Wchnschr. 86:1028, Sept. 15, 1956.

Tes-Tape (Urine Sugar Analysis Paper, Lilly) is recommended. (German)

Langdon, Robert G.; and Weakley, David R. (Dept. of Physiol. Chem., Sch. of Med., The Johns Hopkins Univ., Baltimore, Md.): THE INFLUENCE OF HORMONAL FACTORS AND OF DIET UPON HEPATIC GLUCOSE-6-PHOSPHATASE ACTIVITY. J. Biol. Chem. *214*: 167-74, May 1955.

Dietary and hormonal factors were examined for their effect on hepatic glucose-6-phosphatase activity. Glucose-6-phosphatase activity was increased more than two-fold in the liver of the alloxan-diabetic rat. Insulin in vivo decreased this elevated activity. The liver of the fasted animal showed only a 50 per cent increase in activity. The administration of either cortisone or adrenal cortical extract produced modest, unimpressive increases in hepatic glucose-6-phosphatase activities. In two instances, pituitary growth hormone had no significant effect upon the enzymatic activity.

The physiological significance and possible mechanism for these effects is discussed.

Lasch, H. G.; and Schimpf, K. (Med. Univ. Clinics, Heidelberg, Germany): BLOOD CLOTTING AND ALIMENTARY FAT. Deutsches Arch. klin. Med. *203*:146-51, 1956.

Normal man shows a significant shortening of the clotting time after ingestion of 70 gm. of butter. The peak of this effect is reached about 120 or 150 minutes after the fatty meal. Increases of factor VII and, to a lesser degree, of prothrombin activity are found, and the serum antithrombin appears to be less active. The cause of this decrease in clotting time is most likely an increased activity of thrombokinase. The authors suggest that these observations may have clinical significance. A low-fat diet may be helpful in the prophylaxis and therapy of thrombosis.

Lee, Charles T.; and Duncan, Garfield G. (Pennsylvania Hosp. and Benjamin Franklin Clin., Philadelphia, Pa.): DIABETIC COMA: THE VALUE OF A SIMPLE TEST FOR ACETONE IN THE PLASMA—AN AID TO DIAGNOSIS AND TREATMENT. Metabolism 5:144-49, March 1956.

A serial dilution technic is reported for determining plasma acetone concentration. It is used as a guide to severity of diabetic coma and serves as a means of determining insulin requirements. In particular, the test gives evidence of returning insulin sensitivity and helps to prevent overtreatment.

McKenzie, J. M.; Marshall, P. B.; Stowers, J. M.; and Hunter, R. B. (Dept. of Pharmacol. & Therapeutics, and Dept. of Med., Univ. of St. Andrews, Queen's Coll., Dundee, Scotland): BZ-55 IN DIABETES. Brit. M. J. 2: 448-51, Aug. 25, 1956.

The authors report results of a clinical trial of BZ-55 on twenty diabetic patients.

MacNeal, Perry S.; and Rogers, John (Med. Serv., Pennsylvania Hosp., Benjamin Franklin Clin., Philadelphia,

Pa.): THE COMPLICATIONS OF DIABETES MELLITUS. M. Clin. North America 39:1607-29, November 1955.

The authors presented findings on examination of 103 patients suffering from diabetes mellitus in an attempt to find a common denominator affecting the incidence of complications. Complications studied include cataracts, retinopathy, hypertension, heart disease, renal complications, peripheral vascular disease, neuropathy and glaucoma. The only factors they were able to demonstrate in the statistical analysis which seemed to be important in the development of vascular complications were the age of the patient and the duration of the diabetes. They also concluded from their statistics that good control of the diabetes did not prevent development of retinopathy but did seem to affect its severity. The authors also offer a system of classifying diabetic patients under the headings of Etiology, Degree of Metabolic Fault, Degree of Instability and Secondary Involvement.

Maske, H.; Munk, K.; Homan, J. D. H.; Bouman, J.; and Matthijsen, R. (Medizinischen Universitätsklinik, Munich, Germany, and Wissenschaftlichen Labs. der N. V. Organon, Oss, Holland): THE DISTRIBUTION OF INSULIN AND ZINC IN DIFFERENT CELLULAR FRACTIONS OF THE GIANT ISLETS OF FLOUNDERS AND FLUKES (PLEURONECTIDES). Ztschr. Naturforsch. *11b*:407-415, July 1956.

In order to study the functional relationship between insulin and the zinc content of the pancreatic islets, the authors homogenized and fractionated by centrifugation the giant islets (Brockmann organs) of pleuronectides. Fish islets were chosen for this investigation, because, in this species, the islets are not imbedded in excretoric glandular tissue and therefore can be excised rather easily. The various fractions were analyzed for nitrogen, zinc, insulin and succino-dehydrogenase. The greatest concentration of insulin and zinc was found in the fraction which contained the granular elements and which is generally thought to contain mitochondria and microsomes. The finding of the highest succino-dehydrogenase activity in this same fraction seemed to confirm this assumption. Since insulin content and succino-dehydrogenase activity are parallel in all fractions, it is concluded that insulin is fixed or attached to the mitochondria. The concentration of zinc in the various fractions differs, however, from that of insulin. Yet the zinc found in the mitochondria fraction was calculated as sufficient to hold the insulin in a poorly soluble depot form, particularly if an interaction of proteins is assumed to be involved in the formation of such insulin-zinc-protein depots. Zinc, however, is found also in other fractions in relatively large quantities. On the basis of these data, the authors describe a scheme which might trace the process of insulin secretion.

Mirsky, I. Arthur (Dept. of Clin. Science, Sch. of Med., Univ. of Pittsburgh, Pittsburgh, Pa.): THE ROLE OF INSULINASE AND INSULINASE-INHIBITORS. Metabolism 5:138-43, March 1956.

This report summarizes the evidence that the liver, in particular, contains an insulin-inactivating system, as well as factors for inhibiting the aforementioned system. Data are given which support the hypothesis that insulin insufficiency of diabetes mellitus may be due to an increased rate of insulin destruction.

Mirsky, I. Arthur; Perisutti, Gladys; and Dixon, F. J. (Dept. of Clin. Sci. and Dept. of Path., Sch. of Med., Univ. of Pittsburgh, Pittsburgh, Pa.): THE DESTRUCTION OF I^{131}-LABELED INSULIN BY RAT LIVER EXTRACTS. J. Biol. Chem. *214*:397-408, May 1955.

The effect of a crude extract of rat liver on the degradation of I^{131}-labeled insulin was measured by determination of the proportion of the protein-bound I^{131} which appeared in the nonprotein fraction of the incubation mixture under specified conditions. The specificity of the system responsible for the destruction of insulin (insulinase) was determined by comparison of the effect of the liver extract on I^{131} insulin with that on similarly labeled ribonuclease, pepsin, prolactin, lysozyme, chymotrypsin and human serum albumin. Under conditions which yielded maximal degradation of insulin, no appreciable effect on lysozyme, chymotrypsin, or serum albumin was noted. However, an appreciable degradation of ribonuclease, pepsin, and, to a lesser degree, prolactin occurred. According to the authors, studies on the effect of substrate concentration on the degradation of the different proteins and of the addition of these proteins on the degradation of several concentrations of insulin indicate that the destruction of insulin is due to a specific system (insulinase).

Murray, Ian; and Wang, Ian (Dept. of Metabolic Dis., Victoria Infirmary, Glasgow, Scotland): THE VALUE OF BZ-55 IN CONTROL OF DIABETES. Brit. M. J. 2: 452-54, Aug. 25, 1956.

The authors report a trial of BZ-55 in twenty-five diabetic patients. No satisfactory explanation is given for success or failure with this drug, but it is pointed out that all patients in this series who showed no response had previously received insulin. Ketosis may develop rapidly on the substitution of insulin for BZ-55 in patients who require the insulin for their control.

Parkhurst, Leonard W.; and Betsch, William F. (Benjamin Franklin Clin. and Pennsylvania Hosp., Philadelphia, Pa.): THE INCIDENCE AND DIAGNOSIS OF DIABETES MELLITUS IN A DIAGNOSTIC CLINIC. M. Clin. North America 39:1571-77, November 1955.

The authors reviewed the records of 6,088 consecutive patients in the Benjamin Franklin Clinic for diagnostic evaluation and found 267, or 4.4 per cent, to have diabetes mellitus. The authors discuss the criteria for the diagnosis of diabetes and stress the evaluation of a diagnosis of diabetes in the presence or absence of hepatic disease and other conditions of a nondiabetic nature. They also note that routine urinalysis and fasting blood sugar determinations many times fail to uncover a large number of asymptomatic diabetics. It was also noted by the authors that premature degenerative changes associated with diabetes are oftentimes under way in the asymptomatic diabetic, which makes early diagnosis and treatment, in the hope of retarding these complications, even more important.

Patmalnieks, J.; and Gardell, S. (Chem. Dept. II, Karolinska Inst., Stockholm, Sweden): QUANTITATIVE DETERMINATION OF FRUCTOSE BY MEANS OF A THYMOL-HYDROCHLORIC ACID REAGENT. Scandinav. J. Clin. & Lab. Invest. 8:223-29, 1956.

A colorimetric method for the determination of fructose and other ketoses or ketose-containing oligo- and polysaccharides with a thymol-hydrochloric acid reagent is described. In the range 25-400 mg. per ml., fructose in samples of urine can be determined specifically even in the presence of up to 5 mg. per ml. of glucose and other aldosugars. The method has also been adapted to the determination of fructose in blood following removal of the proteins by trichloracetic acid.

Public Health: A SEARCH FOR DIABETES. Lancet 2:578, Sept. 15, 1956.

The author comments on the result of a recent diabetes detection survey carried out in Salford, England. There were 2,165 urine tests performed with the Clinitest reagent, 150 of which showed positive for sugar. After rechecking, the positive tests were reduced to thirty-one in number. The final outcome was that six previously undetected diabetics (a rate of 2.6 per 1,000) and ten cases of renal glycosuria were identified and referred to their own doctors or to diabetic clinics.

Reinhardt, David J. III; Goldstein, Franz; Jenson, William K.; and Waldron, Jerome M. (Guy's Hosp., London, England; Am. Heart Assoc.; Pennsylvania Hosp., Philadelphia, Pa.): DIABETES MELLITUS WITH DIASTOLIC HYPERTENSION: A STUDY OF THE INCIDENCE, COMPLICATIONS AND MANAGEMENT. M. Clin. North America 39:1631-42, November 1955.

Five thousand cases at the Benjamin Franklin Clinic were reviewed by the authors for the diagnosis of diastolic hypertension and diabetes mellitus. The diagnosis of hypertension was established if the diastolic pressure was over 100 mm. of mercury in persons over forty or over 95 mm. of mercury in persons between twenty and forty years of age. It was found that the incidence of hypertension among diabetic patients and the incidence of diabetes mellitus among hypertensive patients were much higher than the incidence of these diseases among the total cases. A high incidence of obesity was found in both diabetic and hypertensive individuals, but quite a marked increased incidence was found in those who had combined hypertension and diabetes. The incidence of vascular complications was also found to be much higher in the combined group of diabetics and hypertensives than in either one of the groups singly. The authors discuss the management of both the diabetes and the hypertension as separate entities, stressing the fact that good control of both the diabetes and the hypertension is more important when both diseases are present because of the increased potential of the development of vascular complications.

Tunbridge, R. E.; Paley, Ronald G.; and Coulson, Douglas (Dept. of Med., Univ. of Leeds, Leeds, England): ENZYME TEST FOR GLYCOSURIA. Brit. M. J. 2:588, Sept. 8, 1956.

The authors comment on the Tes-Tape (Urine Sugar Analysis Paper, Lilly) method for detecting glycosuria and point out its limitations in clinical practice.

Vander Veer, Joseph B.; and Fisher, George R. (Grad. Sch. of Med., Univ. of Pennsylvania, Pennsylvania Hosp.; Jefferson Med. Coll., Philadelphia, Pa.): FLUID BALANCE AND ELECTROLYTE PROBLEMS IN THE MANAGEMENT OF DIABETIC COMA. M. Clin. North America 39:1587-98, November 1955.

A detailed discussion of the electrolyte problems associated with the management of diabetic coma are presented from a clinical standpoint. Special attention is paid to the problem of potassium depletion associated with the sodium and chloride changes in both the extracellular and intracellular compartments. Several illustrative cases are presented which demonstrate electrolyte problems.

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HARVEY C. KNOWLES, JR., M.D., *Cincinnati*
ARNOLD LAZAROW, M.D., *Minneapolis*
E. PAUL SHERIDAN, M.D., *Denver*

PAST PRESIDENTS

RANDALL G. SPRAGUE, M.D., *Rochester, Minn.*; HENRY B. MULHOLLAND, M.D., *Charlottesville, Va.*; HENRY T. RICKETTS, M.D., *Chicago*

Preliminary Program of the 17th Annual Meeting of the American Diabetes Association

June 1-2, Hotel Commodore, New York City

"Certain Aspects of the Metabolism of Glycogen" is the title of the Banting Memorial Lecture of the American Diabetes Association which will be delivered by DeWitt Stetten, Jr., M.D., at the Seventeenth Annual Meeting. The address will be given during the Scientific Session scheduled for Saturday afternoon, June 1. Dr. Stetten, who is Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland, will be presented with the Banting Medal at the Annual Banquet of the Association to be held that evening. The Banquet will also feature an address by Frederick W. Williams, M.D., President of the American Diabetes Association, and an address by Louis H. Bauer, Secretary General, World Medical Association.

Although a Joint Meeting per se will not be held with The Endocrine Society, this year arrangements have been made so that papers on diabetes and allied subjects (see page 217) will be presented at the session of that Society on Saturday morning, June 1, preceding the opening of the Scientific Sessions of the American Diabetes Association Saturday afternoon. The Endocrine Society Meeting will be held at the Hotel New Yorker and members of the American Diabetes Association will be admitted to that meeting without charge providing they present the ADA registration badge.

Reciprocal arrangements have been made to accommodate members of The Endocrine Society at Scientific Sessions of the American Diabetes Association. Papers of particular interest to them have been scheduled for the Saturday afternoon, June 1, session of the American Diabetes Association. The Endocrine Society's members will be admitted without charge to that session, as well as the following sessions on Sunday, June 2, by registering at the ADA desk.

Printed programs of the American Diabetes Association, containing abstracts of papers to be presented, will be available at the registration desk at $1.00 each. All members will be sent a free copy in advance of the meeting; however, the aforementioned charge will be made for copies secured at the time of registration.

The program of the Seventeenth Annual Meeting follows, including pertinent information about the Scientific Sessions.

Registration:

Friday, May 31: 8:30 a.m.-7:00 p.m.
Saturday, June 1: 8:30 a.m.-5:30 p.m.
Sunday, June 2: 8:30 a.m.-5:30 p.m.

Social Hour: Saturday, June 1, 6:30 p.m.

Banquet: Saturday, June 1, 7:30 p.m.

Annual Business Meeting: Sunday, June 2, 2:00 p.m.

Groups scheduled to convene before the Annual Meeting include: Committees, May 29-31; Council, May 31; Board of Governors, May 31-June 1; Assembly of Delegates, June 1.

SCIENTIFIC SESSION

Saturday, June 1, 2:00 p.m.

FREDERICK W. WILLIAMS, *Presiding*

Preliminary Studies on the Demonstration of Insulin in the Islets by the Fluorescent Antibody Technic

PAUL E. LACY (by invitation), and JACK DAVIES (by invitation), School of Medicine, Washington University, St. Louis, Mo.

The Pathogenetic Mechanism for "Hydropic Degeneration" of the Pancreatic β Cells

SYDNEY S. LAZARUS and BRUNO W. VOLK (by invitation), Isaac Albert Research Institute, Jewish Chronic Disease Hospital and Albert Einstein Medical College, Brooklyn and Bronx, N.Y.

The Role of the Adrenal Cortex in Diabetic Retinopathy and Nephropathy

HAROLD RIFKIN and SEYMOUR LIEBERMAN (by invitation), Montefiore Hospital and The College of Physicians and Surgeons, Columbia University, New York, N.Y.

BANTING MEMORIAL LECTURE

Certain Aspects of the Metabolism of Glycogen

DEWITT STETTEN, JR., (by invitation), Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Influence of the Nephrotic Syndrome on Experimental Diabetes

N. KALANT (by invitation), M. CLAMEN (by invitation), and M. M. HOFFMAN, Jewish General Hospital and McGill University, Montreal, Canada.

A Comparison of Insulin Activity of Serum as Measured by Biologic Assay and Decay of Insulin I-131

GEORGE W. SCOTT (by invitation), THADDEUS E. PROUT (by invitation), JOHN A. WEAVER (by invitation), and SAMUEL P. ASPER, JR., The Johns Hopkins Hospital, Baltimore, Md.

BANQUET

Saturday, June 1, 7:30 p.m.

Invocation by DEACONESS MAUDE BEHRMAN, Director, The Mercer Memorial House, Atlantic City, N.J.

Address by FREDERICK W. WILLIAMS, President
Presentation of the Banting Medal to DEWITT STETTEN, JR., Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Presentation of the Lilly Award to SOLOMON A. BERSON, Chief, Radioisotope Service, Veterans Administration Hospital, Bronx, N.Y.

Presentation of citation to MR. and MRS. C. PAUL TILEY, St. Louis, Mo. MRS. TILEY is President of the St. Louis Diabetes Association and MR. TILEY is Chairman of the Committee on Summer Camps for Diabetic Children

Address by LOUIS H. BAUER, Secretary General, World Medical Association

SCIENTIFIC SESSION

Sunday, June 2, 9:00 a.m.

FREDERICK W. WILLIAMS, *Presiding*

Diabetes Mellitus: Peripheral Vascular Complications in a Survey of 3,600 Cases

DAVID W. KRAMER and PAUL K. PERILSTEIN, Jefferson Medical College Hospital, Philadelphia General Hospital, and St. Luke's and Children's Medical Center, Philadelphia, Pa.

The Occurrence of Diabetes Mellitus in Association with Primary Carcinoma of the Pancreas

ROBERT C. GREEN, JR., ARCHIE H. BAGGENSTOSS (by invitation), and RANDALL G. SPRAGUE, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Paperchromatography, A Simple Method for the Differentiation of Sugars in the Urine

G. R. CONSTAM, Medical Policlinic, University of Zurich, Switzerland

Studies of the Mortality of Diabetic Acidosis

THOMAS G. SKILLMAN (by invitation), J. RODMAN WILSON, JR., (by invitation), and HARVEY C. KNOWLES, JR., University of Cincinnati College of Medicine, Cincinnati.

Studies with Insulin-Binding Antibody

SOLOMON A. BERSON (by invitation), and ROSALYN S. YALOW (by invitation), Radioisotope Service, Veterans Administration Hospital, Bronx, N.Y.

Excretion Patterns of Some B Vitamins in Diabetics with and without Degenerative Complications

JAMES B. FIELD, DANIEL FEDERMAN (by invitation), ERNEST McDANIEL (by invitation), and HOWARD BAKERMAN (by invitation), The National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

PANEL DISCUSSION

Pregnancy

LESTER J. PALMER, Moderator, University of Washington School of Medicine and Virginia Mason Hospital, Seattle, Wash.

WILLIAM P. GIVEN (by invitation), Cornell University Medical College, New York, N.Y.

EDMUND L. SHLEVIN, State University of New York at New York City, College of Medicine

PRISCILLA WHITE, Joslin Clinic and New England Deaconess Hospital, Boston, Mass.

HUGH L. C. WILKERSON, U. S. Public Health Service, Boston, Mass.

SCIENTIFIC SESSION

Sunday, June 2, 2:30 p.m.

JOHN A. REED, *Presiding*

Histochemical Observations on Zinc in the Langerhans Islets of Rabbits after Orinase

HELMUT MASKE (by invitation), University of Munich, Germany. Presently at: Research Laboratories, Veterans Administration Hospital, Denver, Colo.

The Effect of the Sulfonylureas in Chronically Depancreatized Dogs

HENRY T. RICKETTS, HENRY L. WILDBERGER and HANS SCHMID (by invitation), University of Chicago, Chicago, Ill.

Experience with a New Orally Effective Hypoglycemic Compound (Non-Sulfur)

ROBERT H. WILLIAMS, JEAN M. TYBERGHEIN (by invitation), ROBERT L. NIELSEN (by invitation), DONALD C. TANNER (by invitation), and HEIDI H. SWANSON (by invitation), University of Washington School of Medicine, Seattle, Wash.

Clinical Trials with a New (Nonsulfonamide) Hypoglycemic Agent, N^1-8-phenethylformamidynliminourea-HCl (DBI)

LEO P. KRALL and RAFAEL CAMERINI-DAVALOS, Joslin Clinic and New England Deaconess Hospital, Boston, Mass.

PANEL DISCUSSION

Oral Hypoglycemic Agents

ARTHUR R. COLWELL, SR., Moderator, Northwestern University Medical School, Chicago, Ill.

HENRY DOLGER, The Mount Sinai Hospital, New York, N.Y.

GARFIELD G. DUNCAN, Jefferson Medical College of Philadelphia, Philadelphia, Pa.

RACHMIEL LEVINE, Michael Reese Hospital, Chicago, Ill.

MARY K. ROOT, Lilly Research Laboratories, Indianapolis.

BY TITLE

Etiology, Pathology and Treatment of Diabetes Insipidus

HARRY BLOTNER, Boston, Mass.

Preliminary Experiences with D-860 in the Therapeutics of Diabetes Mellitus

ARTURO CABARROU, HECTOR V. CAINO, OSCAR A. PINTADO (by invitation), and NESTOR O. BIANCHI (by invitation), Instituto General San Martin, La Plata, Argentina

Results Obtained in La Plata (Republica Argentina) in the Treatment of 200 Diabetic Patients with BZ-55

HECTOR V. CAINO, ARTURO CABARROU, NESTOR O. BIANCHI (by invitation), and OSCAR A. PINTADO (by invitation), Instituto General San Martin, La Plata, Argentina

The Incidence of "Complications" in a Large Charity Diabetic Clinic

HAROLD L. DOBSON (by invitation), HARRY S. LIPSCOMB (by invitation), JAMES A. GREENE and HUGO T. ENGELHARDT, Houston, Tex.

One Year's Clinical Experience with Orinase Treatment in 500 Patients

HENRY DOLGER and JOHN J. BOOKMAN (by invitation), The Mount Sinai Hospital, New York, N.Y.

Fasting Plasma Amino Acid Values in Older Diabetic Patients

VERNON O. ERK (by invitation), and THOMAS H. McGAVACK, New York Medical College, New York, N.Y.

Present Day Treatment of the Pregnant Diabetic: Success or Failure?

WILLIAM P. GIVEN (by invitation), Cornell University Medical College, New York, N.Y.

Orinase Therapy in the Ambulatory Diabetic Patient

ROY C. GUMPEL (by invitation), WILLIAM STONE (by invitation), ALEXANDER G. VONGRIES (by invitation), and ELAINE P. RALLI, Lenox Hill Hospital and the Third (New York University) Medical Division of Bellevue Hospital, New York, N.Y.

The Specific Capsular and Tubular Basement Membrane Lesion of the Kidney in Diabetes Mellitus

GORDON R. HENNIGAR and WILLIAM PATTERSON (by invitation), Medical College of Virginia, Richmond, Va.

The Role of the Essential Fatty Acids in Lipid Metabolism in the Diabetic, with Particular Reference to Dietary Supplementation with Ethyl Esters of Linoleic Acid, and with Highly Unsaturated Phospholipids

LAURANCE W. KINSELL, GEORGE D. MICHAELS (by invitation), GEORGE FUKAYAMA (by invitation), and STANLEY J. TALPERS (by invitation), (with the technical assistance of SADIE SMYRL, FLORENCE E. OLSON and MARJORIE COELHO), Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Observations on Relationship of Diabetes Mellitus and Nutritional Liver Disease

CARROLL M. LEEVY, Medical Center, Jersey City, N.J.

Clinical Studies with Dextrotest—A Simplified Blood Sugar Test

JAMES M. MOSS, Georgetown University Hospital, Washington, D.C.

The Significance of Glycosuria and the Abnormal Glucose Tolerance Curve During Pregnancy

PAUL PEDOWITZ (by invitation), and EDMUND L. SHLEVIN, State University of New York at New York City, College of Medicine

Serum Glycoproteins in Juvenile Diabetes

R. L. REEVES, J. H. CRAMPTON, HUGH JONES (by invitation), and W. J. STEENROD, JR., University of Washington School of Medicine and The Mason Clinic, Seattle, Wash.

Public Health Aspects of Diabetes, Present and Future

OLIVER E. TURNER, Pittsburgh, Pa.

Evaluation of a New Test for Early Diabetes

ROGER H. UNGER and LEONARD L. MADISON (by invitation), The University of Texas Southwestern Medical School, and Veterans Administration Hospital, Dallas, Tex.

A Comparison of Blood Sugar Analyses by the Folin-Wu and Somogyi-Nelson Procedures

HUGH L. C. WILKERSON, U.S. Public Health Service, Boston, Mass.

Diagnosis of Diabetes: Findings on Glucose Tolerance Test and Meal Tolerance Tests in 328 Individuals

HUGH L. C. WILKERSON, U.S. Public Health Service, Boston, Mass.

THE ENDOCRINE SOCIETY

Saturday, June 1, 9:00 a.m.
Hotel New Yorker, New York City

Diabetes and Metabolism

LAURANCE W. KINSELL and F. D. W. LUKENS, *Chairmen*

Effect of Growth Hormone on Glucose Production, Utilization and Insulin Response in Hypophysectomized Dogs

N. ALTSZULER,* R. STEELE, J. S. WALL and R. C. DE BODO*

Glucose Penetration into Liver

GEORGE F. CAHILL, JR., A. SCOTT EARLE and JAMES ASHMORE*

Glucagon and Renal Function

H. ELRICK, E. HUFFMAN, C. HLAD, N. WHIPPLE and A. STAUB

Introduced by GILBERT S. GORDAN*

The Effect of Insulin on Mucopolysaccharide Turnover in Rat Skin

SARA SCHILLER* and A. DORFMAN

Functional and Morphologic Studies of the Effect of Orinase on the Pancreas

SYDNEY S. LAZARUS* and BRUNO W. VOLK* (invited paper, 20 minutes)

Pentose and Glucose Studies Including Carbohydrate Tolerance Using Intravenous Arylsulfonylureas Substituted for Insulin

THOMAS F. FRAWLEY,* STANTON SEGAL, MARY M. CAMUS and JOSEPH B. FOLEY

Effects on Blood Sugar of a New Potent Hypoglycemic Compound

ROBERT L. NIELSEN,* HEIDI E. SWANSON,* D. C. TANNER* and ROBERT H. WILLIAMS*

Glucose Utilization by the Leucocytes of Patients with Diabetes Mellitus

MARY E. DUMM*

The Adrenal Medullary Response to Insulin Induced Hypoglycemia

ALAN GOLDFIEN,* ROBERT MOORE,* SHEREF ZILELI,* LENORE BOLING* and GEORGE W. THORN*

Effects of Steroids of Noncorticoid Configuration upon Lipid and Carbohydrate Metabolism

GEORGE D. MICHAELS and LAURANCE W. KINSELL*

*Members of the Endocrine Society

Calcium-45 Dynamics in Human Metabolic Bone Disease

ROBERT P. HEANEY and G. DONALD WHEDON*

FIRST LILLY AWARD TO DR. SOLOMON BERSON

Solomon A. Berson, M.D., Chief, Radioisotope Service, Veterans Administration Hospital, Bronx, New York, will be presented with the first Lilly Award at the Annual Banquet of the American Diabetes Association on Saturday, June 1, during the Seventeenth Annual Meeting. The annual Award, supported by Eli Lilly and Company, consists of $500 and a gold medal. Its purpose is to recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

CHANGE IN COMMITTEE NAME

"Informational Committee on Oral Hypoglycemic Compounds" is the name of the Committee formerly known as "Informational Committee on Oral Antidiabetic Compounds." This change was effected at the suggestion of the Chairman at the 1956-57 Interim Council Meeting held Feb. 2-3, 1957, in Columbus.

SIXTH POSTGRADUATE COURSE

The American Diabetes Association will hold its Sixth Postgraduate Course in Diabetes and Basic Metabolic Problems Jan. 22, 23 and 24, 1958, in Atlanta, Georgia. As a matter of general information, Postgraduate Courses are planned to be held in varied parts of the country. This will be the first meeting of the Association ever to be held in the Southeast. Members and others who expect to attend may also wish to take advantage of this Georgia location in planning their winter vacations.

NEW MEMBERS

Active

The following were elected as of Feb. 1 and March 1, 1957:

California

Bonfiglio, Vincent	Los Angeles
Creek, Dale W.	Santa Barbara
Peery, James B.	Fresno

*Member of the Endocrine Society

Connecticut	
Lundberg, George A. F., Jr.	Manchester
District of Columbia	
Ramey, Estelle R.	
Florida	
Peterson, Wesley L.	Sarasota
Georgia	
Clarke, Maurice L. B.	Atlanta
Illinois	
Krahl, Maurice E.	Chicago
Levine, Rachmiel	Chicago
Rhetta, Helen L.	Chicago
Indiana	
Carter, Fred S.	La Porte
Dickson, Dale D.	Greensburg
Kentucky	
Gordon, Armond T.	Louisville
Massachusetts	
Donovan, Robert E.	Arlington
New Jersey	
Robins, Bernard	Hillside
New York	
Leifer, Paul	Bronx
Weisenfeld, Shirley	Brooklyn
Willens, William N.	Bronx
Wormer, Duncan C.	Portville
Ohio	
Chevlen, Harold	Youngstown
Dickie, John D.	Toledo
Mantica, John L.	Steubenville
Merkle, H. Ben	Columbus
Neal, William J.	Archbold
Sellars, Walter S.	Lakewood
Simoson, Leo H.	Cleveland
Tesi, Julius M.	Yorkville
Tucker, Wilson R.	Cincinnati
Pennsylvania	
Buck, Rudolph L.	McKeesport
Everett, Harold E.	Northampton
Joy, Charles A.	Erie
Pellecchia, Patrick E.	Philadelphia
Vester, John W.	Pittsburgh
Rhode Island	
Melucci, Alfred F.	Pawtucket
Virginia	
Hill, Douglass O.	Winchester
Wolfe, Alfred L.	Roanoke

U. S. Possessions

Puerto Rico	
Buxeda, Roberto	Santurce

NEWS OF AFFILIATE ASSOCIATIONS

The CHICAGO DIABETES ASSOCIATION held a meeting on February 22 at the Institute of Medicine of Chicago. Arthur R. Colwell, Sr., M.D., Chairman, Department of Medicine, Northwestern University Medical School, spoke on "Sulfonamides in Diabetes Mellitus," and Rachmiel Levine, M.D., Director, Department of Metabolic and Endocrine Research, Michael Reese Hospital, spoke on "Etiology of Diabetes Mellitus."

The DIABETES ASSOCIATION OF THE DISTRICT OF COLUMBIA sponsored a symposium on "The Sulfonylureas in Diabetes Mellitus" on March 24 in the Auditorium of the Medical Society of the District of Columbia, Washington, D.C. Chairman of the morning session was James M. Moss, M.D., Georgetown University School of Medicine, and Alvin E. Parrish, M.D., George Washington University School of Medicine, was Co-Chairman. The program included the following: "The Historical Development of the Sulfonylureas," by Samuel D. Loube, M.D., George Washington University School of Medicine; "Functional and Histologic Studies Concerning the Action of the Sulfonylureas," by Bruno W. Volk, M.D., Albert Einstein College of Medicine, New York; "The Influence of the Sulfonylureas on the Disposition of Glucose and Pentoses in Man," by Thomas F. Frawley, M.D., National Institutes of Health, Bethesda, Maryland. "The Present Status of Knowledge Regarding the Mechanisms of Action of the Sulfonylureas," by Albert Renold, M.D., Harvard University School of Medicine; "Criteria and Objectives in the Treatment of Diabetes Mellitus," by Alexander Marble, M.D., Harvard University School of Medicine.

The afternoon session was chaired by Louis K. Alpert, M.D., George Washington University School of Medicine, and Aaron G. Saidman, M.D., was Co-Chairman. The following papers were presented: "Experiences with the Sulfonylurea Management of 500 Cases of Diabetes on an Ambulatory Basis," by Henry H. Dolger, M.D., Columbia University, New York; "Clinical Observations in the Treatment of Diabetes Mellitus with the Sulfonylureas," by Samuel J. N. Sugar, M.D., and Lawrence J. Thomas, M.D., both of George Washington University School of Medicine, Dewitt E. DeLawter, M.D., Georgetown University School of Medicine, and Walter L. Henry, M.D., Howard University School of Medicine; "Evaluation of the Side Effects of Tolbutamide," by C. J. O'Donovan, M.D., Kalamazoo, Michigan; and "Summary of the Present Status and Future Potentialities of

the Sulfonylureas in the Management of Diabetes Mellitus," by Alexander Marble, M.D., Harvard University School of Medicine. A panel discussion and a question and answer period were also held.

The NEW YORK DIABETES ASSOCIATION (Clinical Society) held an open meeting February 6 at the New York Academy of Medicine Building in New York City. The following papers were presented: "The Paradoxical Hyperglycemic Effect of Insulin after Cortisone Pretreatment," by Bruno W. Volk, M.D., and Sydney S. Lazarus, M.D., The Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, with Maximilian Fabrykant, M.D., Associate Professor of Clinical Medicine, New York University Post Graduate Medical School, as discussant. A second paper, "Studies with Insulin Binding Antibody," was presented by Solomon A. Berson, M.D., Chief, Radioisotope Service, Veterans Administration Hospital, Bronx, New York, with James B. Field, M.D., Senior Assistant Surgeon, USPHS, National Institutes of Health, Bethesda, Maryland, as discussant. Harold Brandaleone, M.D., Chairman of the Clinical Society, presided.

NEWS NOTES

BANTING MEMORIAL MEETING TO BE HELD JULY 12-13

The Banting Memorial Meeting will be held in Oxford, England, July 12-13, 1957. Prof. H. A. Krebs, Whitley Professor of Biochemistry, University of Oxford, will give the Banting Memorial Lecture entitled "Intermediary Metabolism in the Diabetic Organism."

The program will also include a discussion on clinical results in Britain of trials of the new sulfonamides, and Prof. Charles H. Best, Director, Banting and Best Department of Medical Research, Toronto, Canada, will talk about the experimental and physiological aspects. Other papers on various diabetic subjects will be given.

All communications should be addressed to: The Secretary-General, The British Diabetic Association, 142, Harley Street, London, England. Accommodation will be provided in an Oxford College for those who attend.

R. D. Lawrence, M.D., London, is Chairman of The British Diabetic Association and President of the International Diabetes Federation.

ADA MEMBERS PARTICIPATE IN POSTGRADUATE COURSES ARRANGED BY AMERICAN COLLEGE OF PHYSICIANS

E. PERRY MCCULLAGH, M.D., was a member of the Consulting Committee which conducted a postgraduate course titled "Pathology and Pathologic Physiology in Internal Medicine." The course was held March 25-29 at The Frank E. Bunts Institute of the Cleveland Clinic Foundation, Cleveland, Ohio. Other ADA members who served as Officers of Instruction included HENRY T. RICKETTS, M.D., Chicago, and PENN G. SKILLERN, M.D., Cleveland.

EDGAR S. GORDON, M.D., Madison, Wisconsin, will be a member of the Guest Faculty of a course entitled "Internal Medicine," to be given May 13-17 at the Albert Merritt Billings Hospital, Chicago. Officers of Instruction include HENRY T. RICKETTS, M.D., Chicago, and HENRY L. WILDBERGER, M.D., Chicago.

F. CURTIS DOHAN, M.D., Philadelphia, GARFIELD G. DUNCAN, M.D., Philadelphia, and LEO J. WADE, M.D., New York City, will be Officers of Instruction for a course to be held May 20-24 under the sponsorship of the University of Pennsylvania School of Medicine. The course is entitled "Early Prevention and Detection of Disease."

GRACE A. GOLDSMITH, M.D., New Orleans, will be a member of the Guest Faculty at a course to be held May 20-24 at the Louisiana State University School of Medicine, Shreveport, Louisiana. Other ADA members who will participate include BERNARD M. KALSTONE, M.D., and RICHARD B. LANGFORD, M.D., both of Shreveport.

SHEPARD G. ARONSON, M.D., BENJAMIN I. ASHE, M.D., IRVING P. GRAEF, M.D., HERBERT POLLACK, M.D., and ELAINE P. RALLI, M.D., all of New York City, will serve as Officers of Instruction in "Internal Medicine," a course which will be presented May 27-31 at New York University Post-Graduate Medical School.